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UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES TOWARDS DENDROBINE AND APPLICATIONS OF THIOL ESTERS IN ORGANIC SYNTHESIS

by

PATRICIA ANNE ROSE

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Department of Chemistry

Edmonton, Alberta

Spring 1991

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submitted by **PATRICIA ANNE ROSE** in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

H. J. Liu (Supervisor)

O. Hindsgaul

J. Takats

D. D. Tanner

R. A. Locock

T. G. Back (External)

Date: Oct. 25, 1990

to my parents for their undying support

ABSTRACT

Two main areas of research are contained in this thesis, the first being studies on the total synthesis of dendrobine (**1**), a naturally occurring alkaloid, and the second involving methodology of thiol esters.

Synthetic studies on dendrobine were carried as far as compound **89**, which contained all the carbons required in the dendrobine framework. This compound was built up through the photocycloaddition of piperitone (**32**) with vinyl acetate, followed by formation of alkene **36** *via* a Bamford-Stevens reaction. After an allylic oxidation using selenium dioxide, subsequent oxidation to the ketone and hydrolysis of the acetate, compound **53** was formed. This was reacted with vinylmagnesium bromide through a copper mediated Grignard addition, forming compound **55**. Ruthenium tetroxide oxidation and formation of the methyl ester generated a pair of isomeric diketo esters, **56** and **57**. The four-membered ring was expanded through formation of vinyl alcohol **62**, and reaction with bromine, forming compound **89**.

Two different condensation reactions involving thiol esters were examined in the second chapter of this thesis, namely the Wadsworth-Emmons reaction and the Knovenagel condensation.

Two reagents, **84** and **94**, were tested in the Wadsworth-Emmons type reaction and both were found to react readily with aldehydes and ketones in high yields to form α, β-unsaturated thiol esters. The synthetic applications of these compounds were explored.

S,S'-Diethyl dithiomalonate **101**, was utilized in a Knovenagel condensation. The products of these reactions could be reduced selectively in three different manners to form a series of useful products: the saturated thiol esters, the 1, 3-diols and the primary alcohols.

ACKNOWLEDGEMENTS

Foremost, I would like to express my gratitude for the invaluable assistance and guidance given to me by my supervisor, Professor Hsing-Jang Liu. His enthusiasium for chemistry always made the mountains look more attainable.

I also wish to thank Milan Ralitsch who patiently taught me how to use several instuments over the years, and was ever willing to help out.

The superb technical staff at this University were an invaluable asset, and this work could not have been accomplished without their help: Dr. A. M. Hogg, L. Harrower, D. Morgan, J. Olekszyk and A. Jodhan in the Mass Spectrometry Laboratory, R. Swindlehudrst, D. Formanski and J. Hoyle in the Spectral Services and Microanalytical Laboratories, Dr. T. T. Nakashima, T. Brisbane, G. Bigam, L. Kong and G. Aarts in the NMR Spectroscopy Laboratory, and all the personnel in the Electronics, Glass Blowing and Machine shops.

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LIST OF ABBREVIATIONS

Ac	Acetyl
APT	Attached Proton Test
Ar	Aryl
BSA	bis-(Trimethylsilyl)acetamide
Bu	Butyl
CI	Chemical Ionization
CSA	Camphorsulfonic Acid
d	doublet
DABCO	1,4-Diazobicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DME	1,2-Dimethoxyethane
DMF	*N, N*-Dimethylformamide
DMSO	Dimethylsulfoxide
HRMS	High Resolution Mass Spectrum
LDA	Lithium diisopropylamide
m	multiplet
MCPBA	*meta*-Chloroperoxybenzoic acid
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PDCP	Phenyl dichlorophosphate
q	quartet
s	singlet

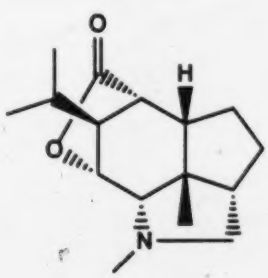
t	triplet
TLC	Thin Layer Chromatography
TOSMIC	*p*-(Tolylsulfonyl)methyl isocyanide
TMSCl	Chlorotrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
p-TsOH	*p*-Toluenesulfonic acid
vt	virtual triplet

CHAPTER I

SYNTHETIC STUDIES TOWARDS DENDROBINE

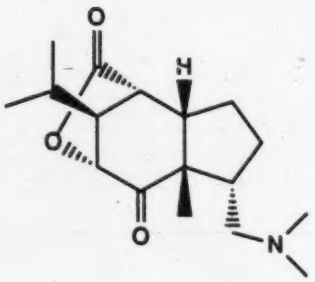
INTRODUCTION

"Chin Shih Hu", an ancient Chinese tonic, was one of many traditional medicines investigated by H. Suzuki and coworkers. In 1932, they isolated dendrobine[1] (**1**) as the main alkaloidal constituent from *Dendrobine nobile* L., an ornamental orchid which constituted a large portion of the tonic. They were able to elucidate the presence of a lactone, an *N*-methyl group as well as the molecular formula through degradation studies, however were unable to determine the actual structure of the compound. The structure remained elusive until 1964, at which time three groups independently determined the molecular structure of this sesquiterpene alkaloid to be as shown below.[2-4]



1

Since 1932, more than fourteen structurally related alkaloids have been isolated from *Dendrobine nobile* L., with nobiline[5] (**2**), dendroxine[6] (**3**), dendramine[7] (**4**) and dendrine[8] (**5**) being a few examples. The unique skeletal structure (a *cis* -hydrindane system with bridged lactone ring) has also been seen in two potent convulsants, picrotoxinin[9] (**6**) and tutin[10] (**7**). Dendrobine itself shows a slight analgesic and antipyretic action;[11]



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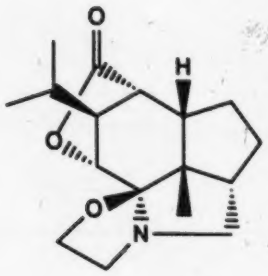

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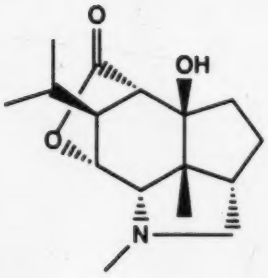

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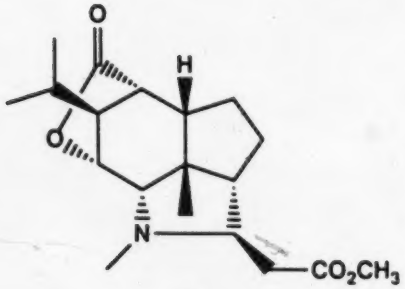

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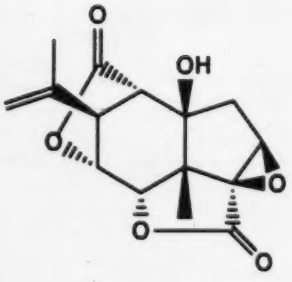

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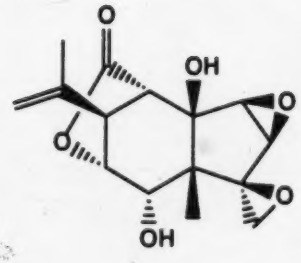


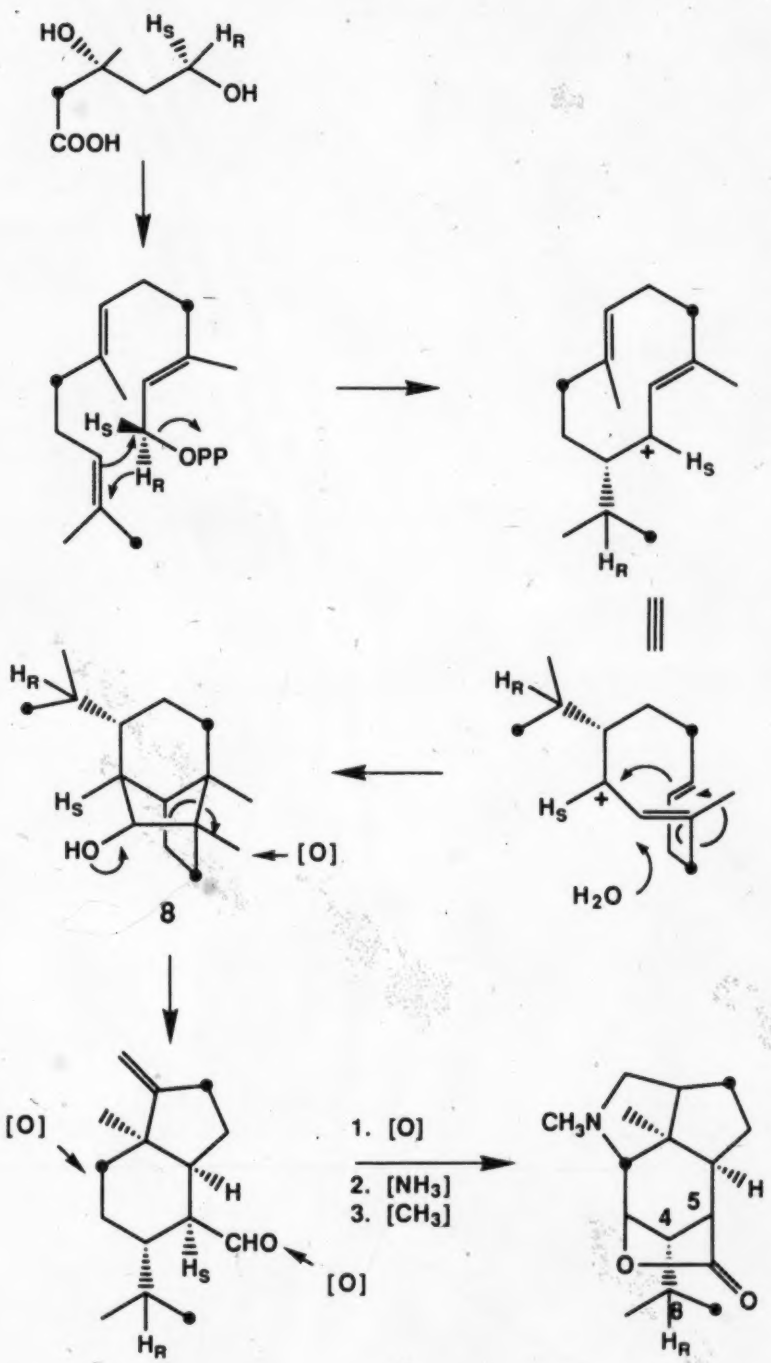
7

however at higher doses causes mammalian toxicity eventually leading to death by convulsion.

Dendrobine has been shown to be derived biosynthetically from mevalonic acid *via* 2-*trans*, 6-*trans*-farnesyl pyrophosphate[12] (see Scheme 1). This was shown in feeding experiments where 2-*trans*, 6-*trans*-farnesol was found to be incorporated while 2-*cis*, 6-*trans*-farnesol was not. Its skeleton does not obey the first order isoprene rule, but is generated through secondary fissions of a germacrene intermediate, **8**. The stereospecificity of the key 1,3 H_R shift proposed in the pathway was shown in the following manner. Labeled [1-$^3H_2$]-2-*trans*, 6-*trans*-farnesol fed to *Dendrobine nobile* L., showed an incorporation of the label of 52% at C-5 and 47% at C-8. This showed unambiguously that the hydrogen atom at C-8 of dendrobine originated from C-1 of farnesol. Feeding of (1S)-[^{3}H]-2-*trans*, 6-*trans*-farnesol revealed 88% recovery at C-5, showing that the 1-*pro*-R hydrogen was being transfered preferentially.

Dendrobine contains a complex tetracyclic system: small, compact yet containing seven stereogenic centers. These challenging features, along with its strong biological properties, have prompted four total syntheses,[13-18] one formal synthesis,[19] two approaches to the skeleton,[20,21] one synthesis of an epimer[22] as well as our own work towards this highly functionalized molecule. Details of the total syntheses, the formal synthesis and our own work are outlined below.

SCHEME 1

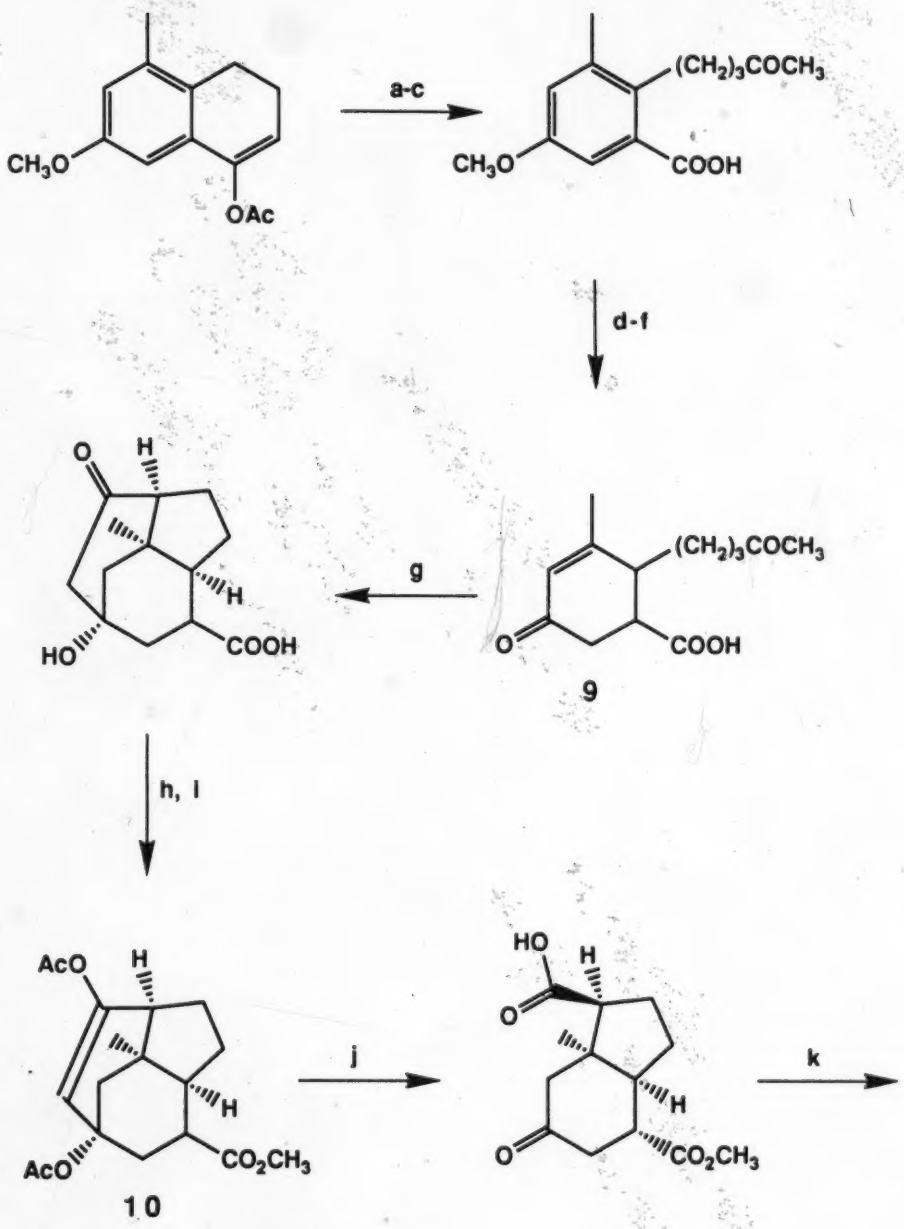

HO
H_S
H_R
OH
COOH
H_S
OPP
H_R
+
H_S
H_R
H_R
H_S
+
H_2O
H_R
H_S
HO
[O]
8
[O]
H
CHO
H_S
[O]
H_R
1. [O]
2. [NH_3]
3. [CH_3]
CH_3N
H
5
4
O
O
H_R

The first total synthesis of dendrobine was reported by K. Yamada in 1972.[15] His group constructed the *cis*-hydrindane system utilizing an intramolecular Michael addition as the key step (see Scheme 2).

The required intermediate (**9**) was formed from 3,4-dihydro-7-methoxy-5-methyl-1(2H)naphthlalenone through ozonolysis of the double bond, extension of the side chain by two carbons and subsequent Birch reduction. The Michael addition was carried out under basic conditions, allowing compound **9** to cyclize to a mixture of epimeric acids, separable by fractional crystallization. Both epimers had the desired *cis*-ring stereochemistry for the hydrindane system. The cyclization also generated a third ring, which was opened through ozonolysis of enol acetate **10**. At this point, the pyrrolidine ring was incorporated by initially forming an amide *via* the imidazole, which spontaneously cyclized to the lactam **11**. Bromination followed by re-cyclization to the pyrrolidone gave the desired A-B-C ring system. Final conversion to dendrobine was carried out through introduction of the isopropyl group by forming the enolate ion and acylating with methyl formate. This generated a mixture of compounds **12** and **13**, the former being converted into the latter using diazomethane. Reaction with *n*-butyl mercaptan formed the thioether, which could be converted to the isopropyl group using lithium dimethylcuprate.

Formation of the lactone ring was carried out by reduction of the keto group and isomerization of the ester, which then spontaneously cyclized to the lactone. Finally, (±)-oxodendrobine was reduced to dendrobine *via* sodium borohydride reduction of the imino ether fluoroborate.

SCHEME 2



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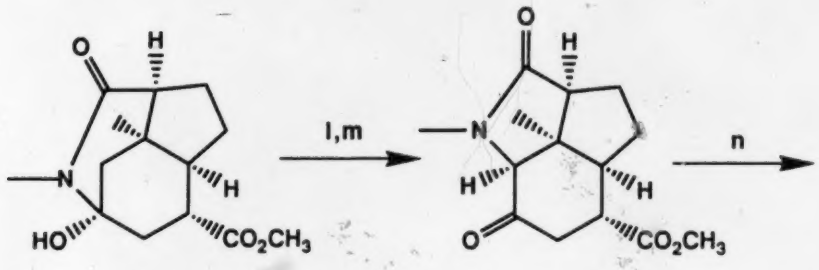

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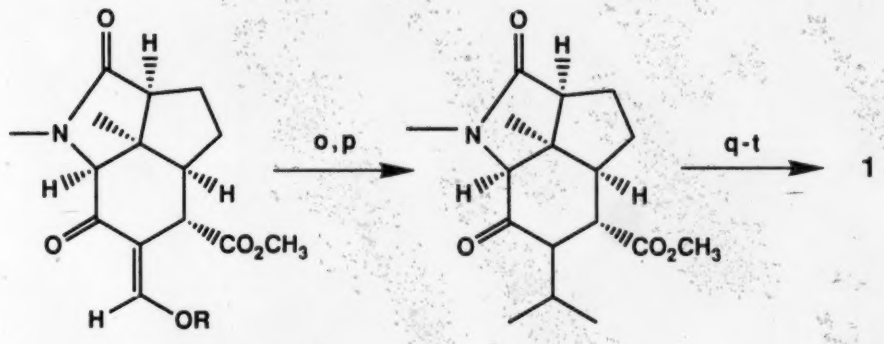


12 R = H
13 R = CH_3

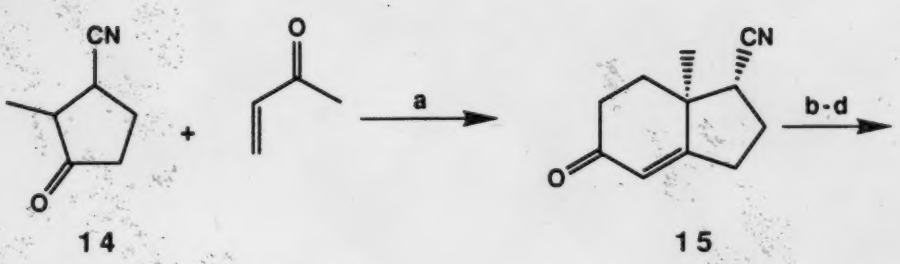
(a)O_3–MeOH; Me_2S, -75°C; hydrolysis; (b) $Ph_3P^+CH(OMe)CH_3$ Cl^-, methyl sulfinyl carbanion, DMSO, -40°C; (c) aq $(COOH)_2$; (d) $(CH_2OH)_2$, H^+; (e) Li, NH_3; (f) aq $(COOH)_2$; 1:1 EtOH-0.4*N* HCl; (g) *tert*-BuOK; (h) CH_2N_2; (i) Ac_2O, CSA; (j) O_3; H_2O; (k) *N,N'*-carbonyldiimidazole; $MeNH_2$-glyme; (l) pyridinium bromide perbromide; (m) NaH, glyme; $(COOH)_2$; (n) HCOOMe-NaOMe-benzene; CH_2N_2;(o) $CH_3(CH_2)_3SH$, CSA; (p) $LiCu(Me)_2$, ether; (q) NaH, glyme; (r) $NaBH_4$; (s) $(C_2H_5)_3OBF_4$, CH_2Cl_2; (t) $NaBH_4$-glyme.

The following year, Inubushi completed the second total synthesis of dendrobine.[13] The *cis*-hydrindane system was built up through an intermolecular Michael addition (see Scheme 3).

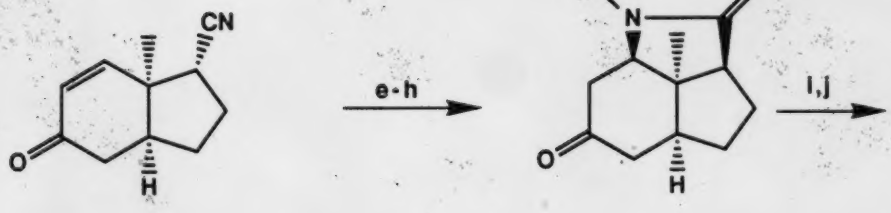
Thus, 3-cyano-2-methylcyclopentanone (**14**) and methyl vinyl ketone were condensed under acidic conditions to form compound **15** in high yield. Hydrogenation and re-introduction of the double bond to the desired position *via* bromination and dehydrobromination generated the enone system **16** as well as reforming compound **15**, which could be recycled. After ketalization, the cyano group was hydrolyzed to form the ketal acid. Under acidic conditions, deketalization and lactonization occurred to form the keto-lactone which was then transformed into the keto-lactam through reaction with 30% aqueous methylamine. Grignard addition of isopropylmagnesium bromide to the carbonyl formed the tertiary alcohol which could be dehydrated to form a mixture of olefins **17**. These were transformed into the allyl acetates which could be easily hydrolyzed and oxidized to a mixture of isomeric enones. The lactone ring was then introduced by 1,4-addition of a nitrile group to the desired enone, followed by hydrolysis to the acid and methylation to form the keto-ester. (±)-Oxodendrobine was formed by first reducing the ketone with sodium borohydride and then hydrolyzing the ester to the acid. Upon acidification, the lactone closed to generate oxodendrobine. This was transformed into dendrobine in a manner similar to Yamada's.

The same year, Andrew Kende developed a pathway to (±)-dendrobine which was designed in such a way as to also provide a route to dihydro-

SCHEME 3



14 15



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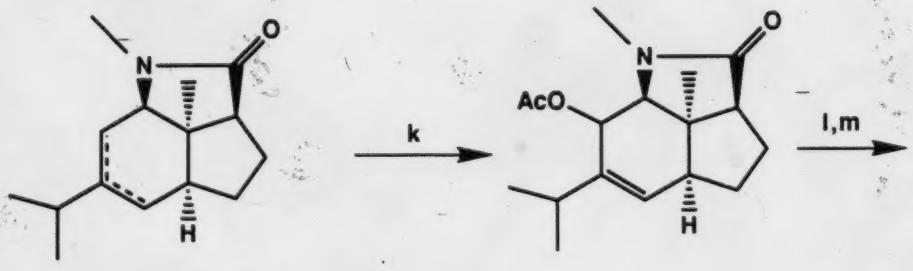

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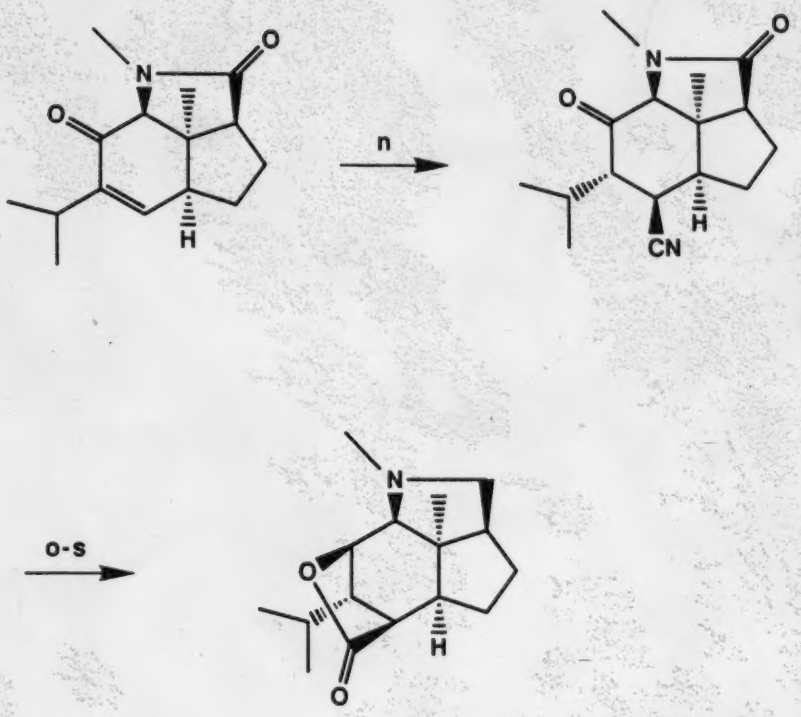
SCHEME 3 (contd.)



(a) *p*-TsOH; (b) H_2/Pd-$SrCO_3$; (c) Br_2; (d) LiBr-Li_2CO_3; (e) $(CH_2OH)_2$, H^+; (f) KOH; (g) aq HCl; (h) aq. $MeNH_2$-$MeNH_3Cl$; (i) $(CH_3)_2CHMgBr$; (j) $KHSO_4$; (k) I_2-CH_3COOAg, AcOH; (l) aq. MeOH-KOH; (m) CrO_3-pyridine; (n) $(CH_3CH_2)_2AlCN$; (o) H_2SO_4-AcOH; CH_2N_2 (p) $NaBH_4$; (q) KOH; HCl; (r) $(CH_3CH_2)_3OBF_4$; (s) $NaBH_4$.

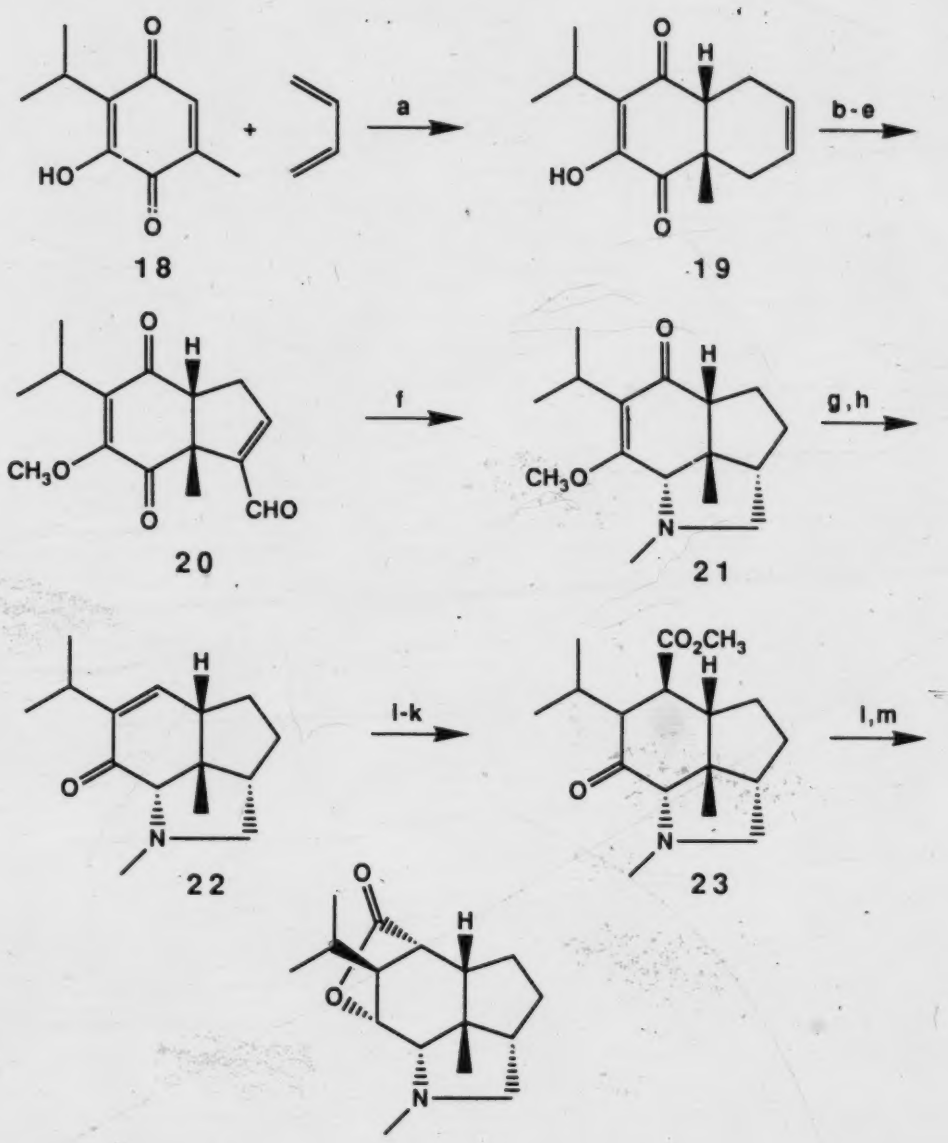
picrotoxinin.[16] He generated the *cis*-hydrindane system through a Diels-Alder reaction followed by a ring contraction (see Scheme 4).

Saponification and ferric chloride oxidation of 1,3,4-triacetyl-2-isopropyl-5-methylbenzene formed dienophile **18** which readily reacted with butadiene to form the Diels-Alder adduct **19** in a 95% yield. After protection of the alcohol, the isolated double bond was cleaved through the diol and then recyclized to the ring contracted product as a 1:1 mixture of regioisomers. The required regioisomer, aldehyde **20**, was then used to introduce the pyrrolidine ring through a reductive amination process which performed a number of crucial steps, forming compound **21**, albeit in low yield (35%). A further 30% of the reaction mixture was the simple reduction product (the alcohol) which could be easily recycled.

Ring A was suitably functionalized by formation of the enone **22** through reduction of the ketone and hydrolysis of the methyl ether, which then rearranged to the enone system. This was followed by 1,4-addition of lithium divinylcuprate, ruthenium tetroxide oxidation and methylation of the resultant acid. After isomerization compound **23** could be reduced and cyclized to the lactone, giving (±)-dendrobine.

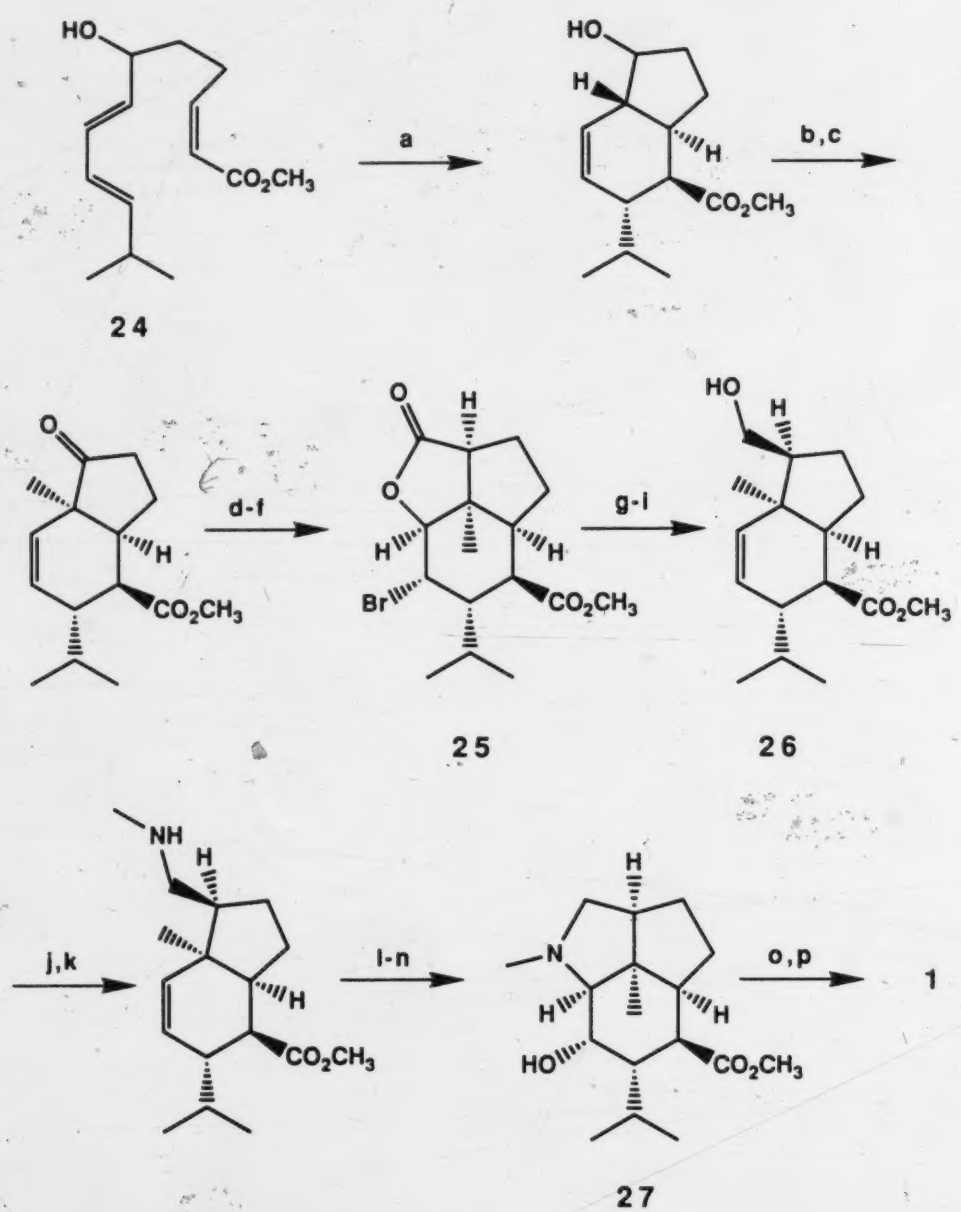
The final two syntheses, one total and one formal, both incorporated an intramolecular Diels-Alder reaction to generate the ring system, however in two very different manners. The first was by William Roush in 1980[18] (see Scheme 5).

SCHEME 4



(a) 110°C, 24 h; (b) MeI, K_2CO_3; (c) OsO_4, $Ba(ClO_3)_2$; (d) H_5IO_6; (e) pyrrolidine acetate; (f) CH_3NH_3Cl, $NaCNBH_3$; (g) $LiAlH_4$; (h) 2N H_2SO_4; (i) lithium divinylcuprate; (j) RuO_4; (k) CH_2N_2; (l) 0.3M NaOMe; (m) $NaBH_4$.

SCHEME 5

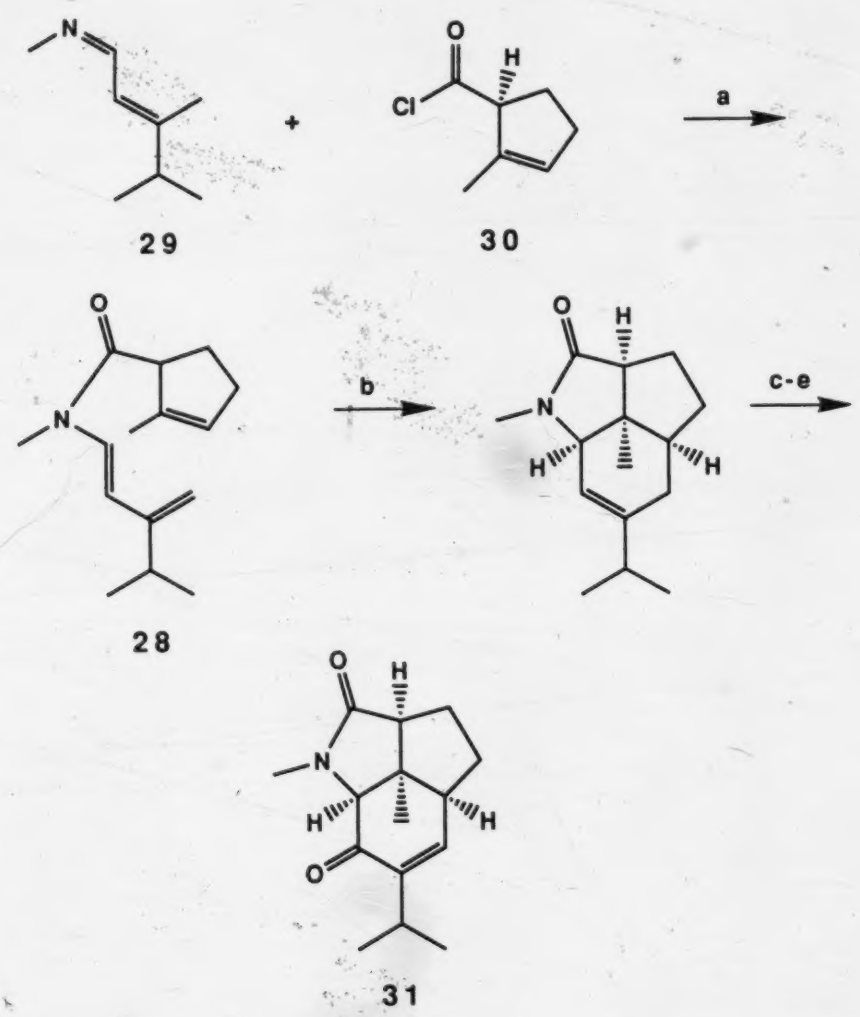


(a) BSA; sealed tube, 115°C; MeOH, 1N HCl; (b) $(CF_3CO)_2O$, DMSO; (c) MeI, KO-*t*-Bu; (d) TOSMIC, KO-*t*-Bu; (e) H_2O_2, NaOH; (f) NBS, H_2O; (g) Zn, HOAc; (h) $(COCl)_2$; (i) $LiAlH(O\text{-}t\text{-}Bu)_3$; (j) CH_3SO_2Cl, Et_3N; (k) Me_2SO, CH_3NH_2; (l) trichloroethyl chloroformate, pyridine; (m) MCPBA; (n) Zn dust, HOAc; (o) H_2CrO_4; (p) $NaBH_4$.

Roush generated the *cis*-hydrindane system and at the same time set the stereochemistry of four centers by the intramolecular Diels-Alder reaction of compound **24**. Swern oxidation of the resultant bicyclic alcohol generated the *trans* fused bicyclic ketone, which isomerized to the *cis* fused ring junction during silica gel chromatography. The newly formed carbonyl was then used to introduce a methyl group through alkylation with methyl iodide, giving the desired regio- and stereochemistry. Extensive functional group manipulation was required to introduce the methylene amine group onto the 5-membered ring. First, introduction of a nitrile group was carried out using tosylmethylisocyanide. Hydrolysis to the amide and oxidation with wet *N*-bromosuccinamide afforded bromolactone **25**. The bromolactone was reduced to the acid alkene with zinc and subsequently reduced through the acid chloride using lithium tri-*tert*-butoxyaluminum hydride to give alcohol **26**. The corresponding amine was formed *via* the mesylate with methylamine. The pyrrolidine ring formed through nucleophilic attack of the amine on the epoxidized double bond by first protecting the amine and reacting the alkene with *meta*-chloroperoxybenzoic acid to form compound **27**. Inversion of the resultant alcohol by oxidation and subsequent reduction back to the alcohol led to the formation of the lactone ring, completing the synthesis.

Finally, in 1989, S. Martin published a highly convergent formal synthesis of dendrobine[19] (see Scheme 6). The key step involved an intramolecular Diels-Alder reaction which not only set the stereochemistry at four centers, but also generated the tricyclic ring system with incorporation of the pyrrolidine ring. The desired intermediate **28** was formed from imine **29** and acid chloride **30**. The Diels-Alder reaction was carried out under

SCHEME 6

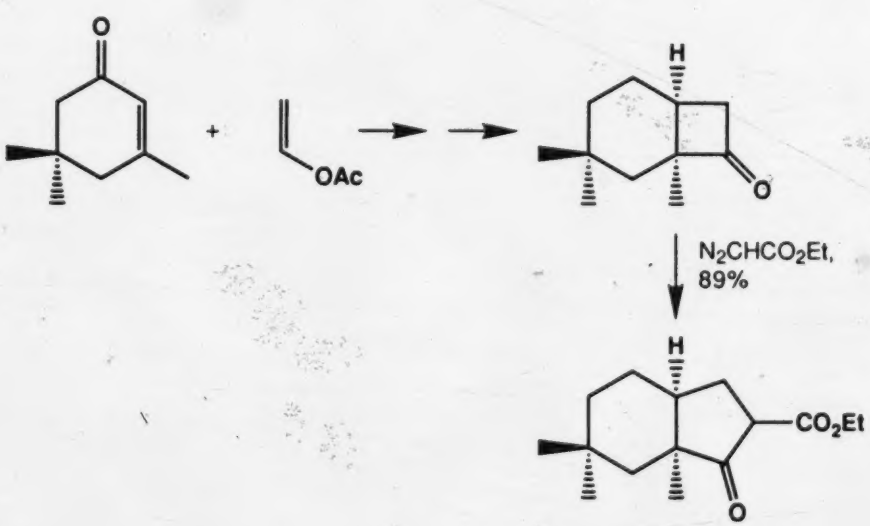


(a) $C_6H_5NEt_2$, toluene; (b) xylenes, 180°C, 10 h; (c) MCPBA; (d) TMSOTf, 2,6-di-*tert*-butyl-4-methylpyridine; (e) PDC.

thermal conditions, forming an 8:1 mixture of two separable adducts with the major product having the desired stereochemistry. The adduct was transformed into Inubushi's key intermediate **31** through epoxidation followed by rearrangement of the epoxide with trimethylsilyl triflate. Oxidation of the resultant alcohol afforded the enone, thus completing the formal synthesis.

Our initial strategy for forming the *cis*-hydrindane ring system was built on a method developed in our laboratory by Ogino in 1973.[23] It involved a 2+2 photocycloaddition and subsequent ring expansion using ethyl diazoacetate. He utilized the photoadduct of isophorone and vinyl acetate, transformed it into the four membered ring ketone and then formed the ring expanded product in 89% yield by reaction with ethyl diazoacetate (see Scheme 7). The success of this method led us to pursue the same strategy for dendrobine.

SCHEME 7



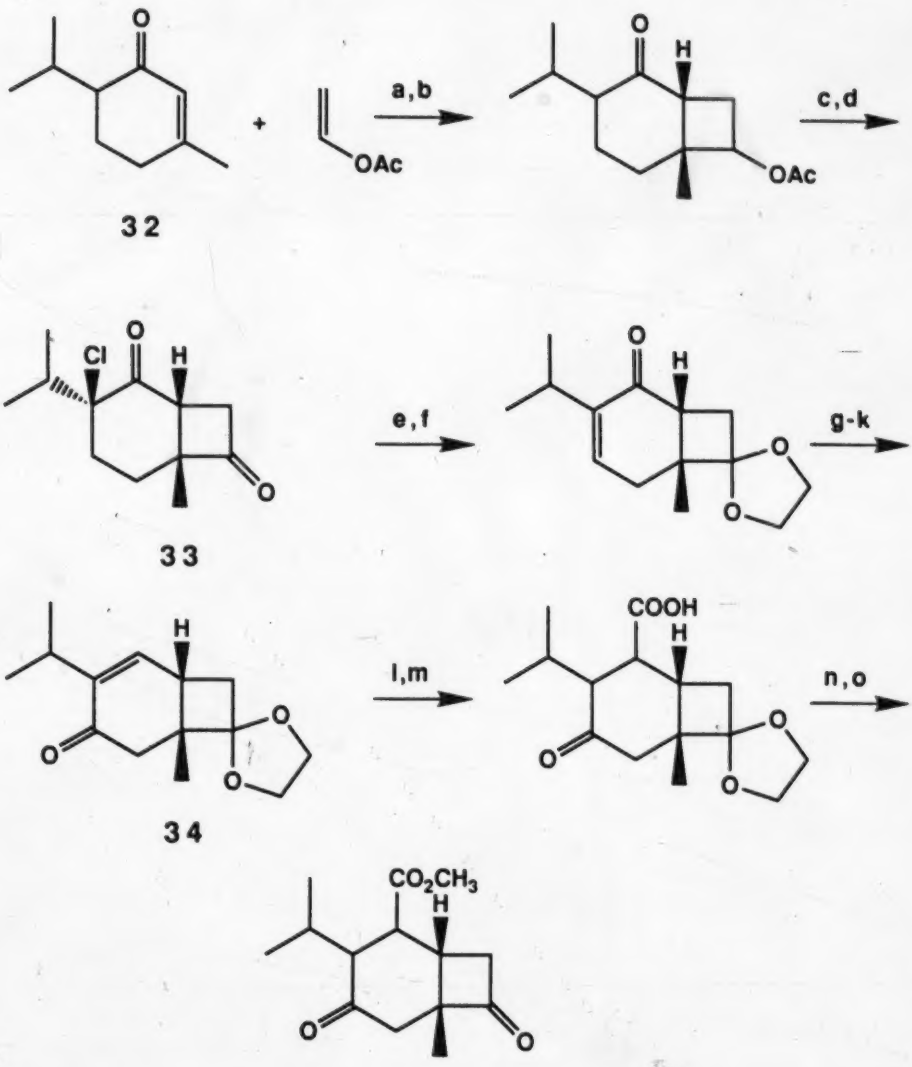
The initial studies on dendrobine were carried out by Nelson.[24] He progressed to the stage of the ring expansion through the following route (see Scheme 8).

Piperitone (**32**) was photolyzed with vinyl acetate and the major isomer was hydrolyzed and then oxidized to compound **33** *via* a Swern oxidation. The introduction of the chlorine α to the six-membered ring carbonyl was an unexpected, yet useful occurrence which has subsequently been studied in our group.[25] Dehydrochlorination was followed by a selective ketalization of the four-membered ring ketone. A 1,3-oxygen transposition through a rather extensive route generated compound **34.** Copper mediated 1,4-addition of vinylmagnesium bromide followed by oxidative cleavage of the resultant vinyl group using ruthenium tetroxide formed a mixture of carboxylic acids. These were transformed into the methyl esters using methyl iodide. Deprotection of the four membered ring carbonyl generated two isomeric diketone esters **35** which were used to investigate the ring expansion reaction.

The synthesis of dendrobine was reexamined at this point and after applying this route for several months, we decided to alter the synthesis to avoid the lengthy 1,3-oxygen transposition, as well as the protection and deprotection steps (see Scheme 9).

Therefore, after building up the A-B ring system through the 2+2 photocycloaddition, alkene **36** was formed and used to carry out an allylic oxidation. The enone system could then be generated in a more efficient manner, allowing for a shorter route to the key intermediate, diketone **35**.

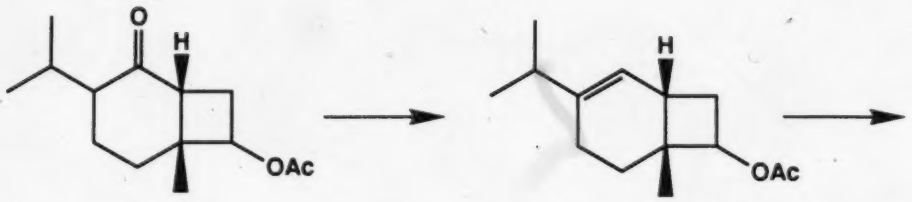
SCHEME 8



(a) hυ; (b) DBU; (c) K_2CO_3, aq MeOH; (d) $(COCl)_2$, DMSO, Et_3N; (e) TMSCl, Et_3N, DMF; (f) $(CH_2OH)_2$, *p*-TsOH; (g) $NaBH_4$; (h) MeI, NaH; (i) B_2H_6; H_2O_2, OH^-; (j) PDC; (k) DBU; (l) vinylmagnesium bromide, CuI; (m) RuO_4; (n) MeI, K_2CO_3; (o) aq. *p*-TsOH.

Several studies were carried out on a model compound which led to the development of a successful method for the ring expansion towards the dendrobine framework. Full details of the development of this route are described in the results and discussion section of this chapter.

SCHEME 9

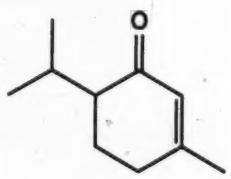


36

35

RESULTS AND DISCUSSION

In order to build up the A-B ring system of dendrobine, we required a photoadduct which would incorporate as many features of the A-ring as possible. Piperitone (3-methyl-6-isopropyl-2-cyclohexen-1-one, **32**), a naturally occurring terpenoid present in Eucalyptus oil, seemed to contain the important requirements: the enone system for the 2+2 photocycloaddition; the isopropyl group; and the ring junction methyl group. Piperitone is also available in both optically active forms, which opened the possibility for a chiral synthesis.

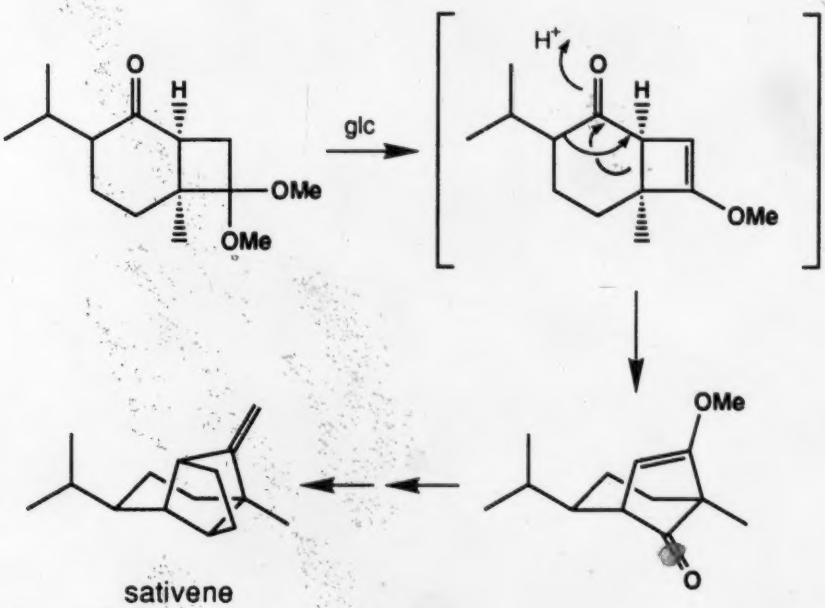


32

Piperitone could easily be generated from commercially available *trans*-piperitol through a Jones oxidation,[26] or alternatively through Birch reduction[27] of the methyl ether of thymol (2-isopropyl-5-methylanisole). The former method was the one of choice and could be carried out in 70-75% yield on a large scale. The enone system showed a stretch at 1668 cm^{-1} in the infrared spectrum and the proton on the double bond showed a peak at δ 5.84 in the ^1H NMR spectrum. Mass spectroscopy also confirmed the structure with a molecular ion peak at 152.1204 for the formula $C_{10}H_{16}O$. Unfortunately, the optical activity of the enone was inconsistent and low ($[\alpha]_D^{22}$ = -20 to -30°), whereas optically pure

piperitone has a rotation of $[\alpha]_D^{22}$ = -77.5°. The low optical activity of the crude piperitol available was the leading factor for this result. As the enantiomeric excess of the piperitone was so low, all subsequent compounds were treated as racemic mixtures.

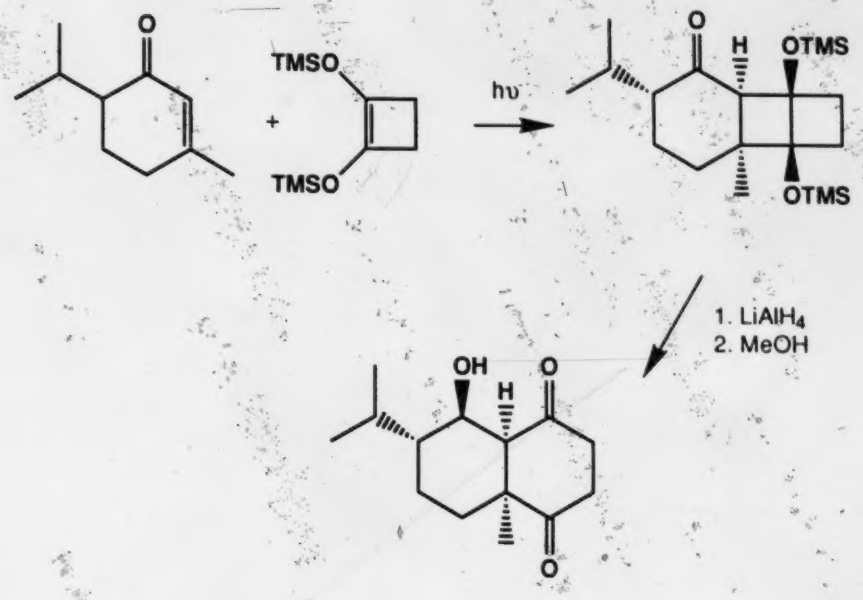
Piperitone has been used previously in photocycloaddition reactions with positive results. For example, Matsumoto used the photoadduct of piperitone and 1,1-dimethoxyethylene in a total synthesis of sativene and related compounds.[28] The key step was the rearrangement of an intermediate vinyl ether which was formed on the glc column (see Equation 1).



sativene

Eq. 1

Piperitone has also been used by Vandewalle in the formation of *cis*-decalin systems through cleavage of the silyl ethers, as seen in Equation 2.[29]



Eq. 2

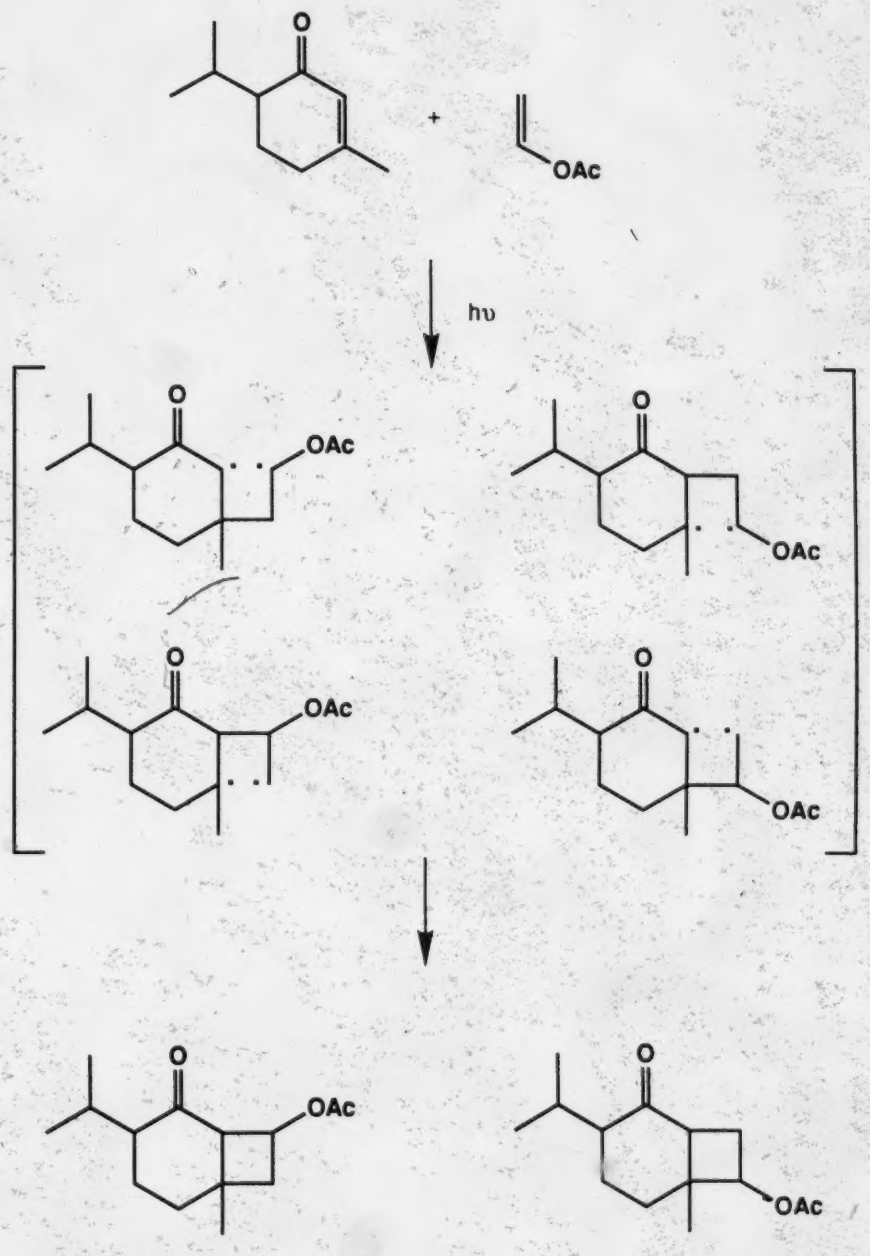
Nelson had studied the photocycloaddition reaction of piperitone with allene, 1,1-dimethoxyethylene, and vinyl acetate. The latter was the most convenient reagent to use as it was commercially available and gave reasonable results. Allene typically gives the opposite regiochemistry to what we desired,[30] whereas 1,1-dimethoxyethylene requires several steps to produce.

The vessel used for the photocycloaddition reaction contains a 450 W mercury vapor lamp sheathed in a pyrex filter which is surrounded by a

quartz cooling jacket. The outer container is equipped with a condenser and contains a sintered glass plug for introducing argon into the system. The entire apparatus is kept ice-cold in a large Dewar flask throughout the reaction. During the photocycloaddition reaction, one wants to excite only one of the substrates (the enone) and have a high concentration of the second substrate to avoid self-condensation of the enone. For this reason, 15 equivalents of vinyl acetate and one equivalent of piperitone were used in this reaction.

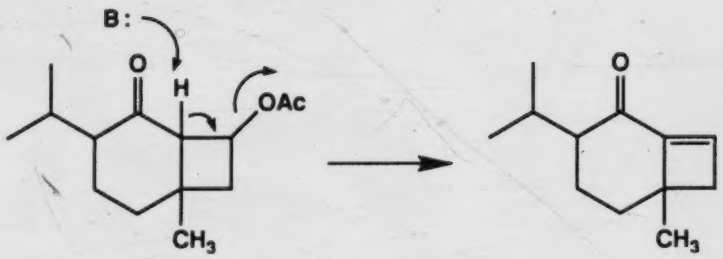
The possibility exists for the formation of a multitude of products during the 2+2 photocycloaddition reaction. Two sets of regiochemical isomers, the head-to-head adduct **37** and head-to-tail adduct **38** can be formed. Each of these regioisomers can form four diastereomers where the ring juncture is *cis*, and the formation of the *trans* ring junction is also concievable, as shown by Corey in 1964.[31] One explanation for these products involves a non-concerted mechanism involving several 1,4-diradical intermediates, which allows for isomerization of all four corners of the cyclobutane ring (see Equation 3).

In order to simplify the purification, the crude reaction mixture is typically refluxed with DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) for 24 hours. This not only isomerizes any *trans* compound but also destroys the head-to-head adduct through elimination of acetic acid and thermolytic cleavage of the resultant cyclobutene (see Equation 4).



37 **38**

Eq. 3



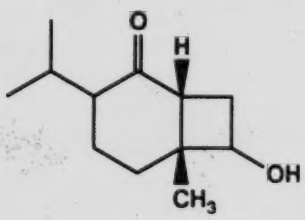
Eq. 4

The proton NMR spectrum showed the necessity of this step, as the initial crude reaction mixture showed more than 7 multiplets between δ 4.5 and 5.5 for the protons adjacent to the acetate units of the various isomers. After treatment with DBU, only three major peaks were observed in this region, with two compounds having overlapping signals as four peaks could be discerned by the ring junction methyl groups. These four peaks were used to determine the ratio of isomers I-IV as being 4.5:2.8:2.2:1, respectively, in a total of 50% yield as determined by column chromatography. The first two isomers could be separated cleanly; however, isomers III and IV were an inseparable mixture.

Isomer II showed spectral data typical of all four isomers. Two carbonyl bands were present in the infrared spectrum, one at 1741 cm^{-1} for the acetate carbonyl and one at 1705 cm^{-1} for the ketone. The ^1H NMR spectrum showed a distinctive peak for the hydrogen adjacent to the acetate unit at δ 4.78 as a triplet with a coupling constant of 8 Hz. This was coupled with the methylene hydrogens on the cyclobutane ring, one of which showed a ddd at δ 2.67 (J = 2.5, 8, 11.5 Hz) and the other a ddd at δ 2.28 (J = 11, 8, 11.5 Hz). Electron impact mass spectroscopy did not show

a molecular ion peak for any of the isomers; however, it did pick up a major peak at 178.1359 for the formula $C_{12}H_{18}O$ corresponding to a loss of acetic acid. Chemical ionization did give the correct molecular weight, $(M+NH_4)^+$ showing at 256.

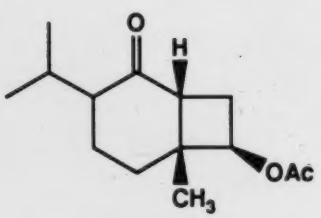
The stereochemistry around the isopropyl group could not be easily determined, and since that chiral center was to be destroyed, we did not pursue the matter. However, the first two acetates were found to be epimeric at the isopropyl group by studying the hydrolyzed derivatives. The acetates could be easily hydrolyzed in nearly quantitative yields using potassium carbonate in aqueous methanol. Both isomers I and II formed the same two alcohols **39** upon hydrolysis, due to concurrent isomerization of the isopropyl group under the reaction conditions. Hydrolysis of the mixture of isomers III and IV formed a separable mixture of alcohols which were isomeric at the isopropyl group. Therefore, isomers I and II had the same configuration around the acetate group, as did isomers III and IV showing them to be diasteriomeric pairs.



39

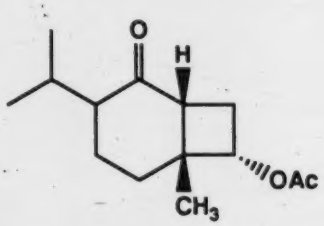
A further study into the stereochemistry came from comparing the shift of the ring junction methyl groups of the hydrolyzed compounds in $CDCl_3$ and pyridine-d_5.[32] Vicinal groups which are cisoidal to hydroxyl groups

show a distinct downfield shift in pyridine as hydrogen bonding of the solvent to the hydroxyl group creates a deshielding zone for the vicinal group to reside in. This was applied to the four hydroxy ketones used in the isomerization studies. The two alcohols from isomers I and II of acetate **38** both showed a large shift (δ 1.25 ($CDCl_3$) to 1.45 (pyridine-d_5) and 1.28 ($CDCl_3$) to 1.44 (pyridine-d_5)). Conversely, the hydrolysis products of isomers III and IV of acetate **38** showed no change in the shift of the methyl group. This showed the relative stereochemistry between the ring junction and the acetate as being *cis* for isomers I and II and *trans* for isomers III and IV of the photocycloadditon products. A further proof is shown at a later stage of the synthesis with NOE studies on alkene **36** and its isomer.



I and II

38



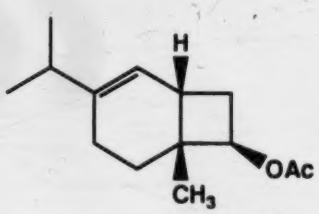
III and IV

38

At this point, two routes were available for building up the ring expanded product. The four-membered ring could first be expanded, and then the A ring could be modified to incorporate the lactone or *vice versa*. Expanding the B ring first would be a desirable route, as large amounts of material would be available early in the synthesis for a step which was already known to cause some difficulties. However, it would also involve several

protection and deprotection steps, and modification of the A ring in the presence of the functional groups on a newly expanded B ring could cause some trouble. Conversely, the acetate unit present in the photocycloadditon product acts as a protecting group for the four-membered ring, thus opening an avenue for easy manipulation of the A ring.

Alkene **36** became the target molecule which would set up the A ring for an allylic oxidation to form the enone system. In this manner, a parallel route to the previous work of 1,4-addition of a vinyl group to an enone system and subsequent oxidative cleavage to the acid could be utilized.



36

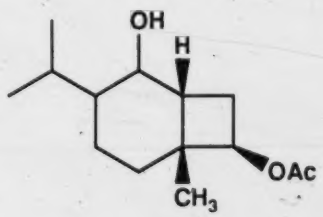
Several methods were available for the formation of alkenes from ketones, the most straightforward being reduction to the alcohol followed by a dehydration step. As the stereochemistry around the isopropyl group was to be destroyed, isomers I and II of acetate **38** were both studied.

Reduction of the ketone was smoothly carried out using sodium borohydride in ethanol at -10°C. These conditions were the most effective in eliminating cleavage of the acetate unit. Isomer I formed two alcohols

(**40**) in 90% yield in a ratio of 85:15. The major alcohol showed a strong O-H band at 3520 cm^{-1} in the infrared spectrum, along with a carbonyl stretch for the acetate at 1737 cm^{-1}. A distinctive proton at δ 4.06 appeared in the ^1H NMR spectrum for the proton adjacent to the hydroxyl group. Again, chemical ionization was required to see the molecular ion peak, which came at 258 as the ammonium ion.

Isomer II of acetate **38** was reduced under the same conditions, forming a 1.4:1 mixture of alcohols in 70% yield. The lower yield was due to contamination of isomer II with isomers III and IV as well as piperitone, due to the very difficult separation involved.

The formation of four different alcohols complicated the dehydration step as the different orientations of the isopropyl and hydroxyl groups would either hinder or assist the elimination step. As the major alcohol from isomer I was the predominant isomer, any useful method would have to dehydrate it cleanly, therefore it was the first isomer investigated.



40

The major alcohol could be dehydrated in 86% yield by reaction with 2 equivalents of thionyl chloride and 4 equivalents of pyridine in

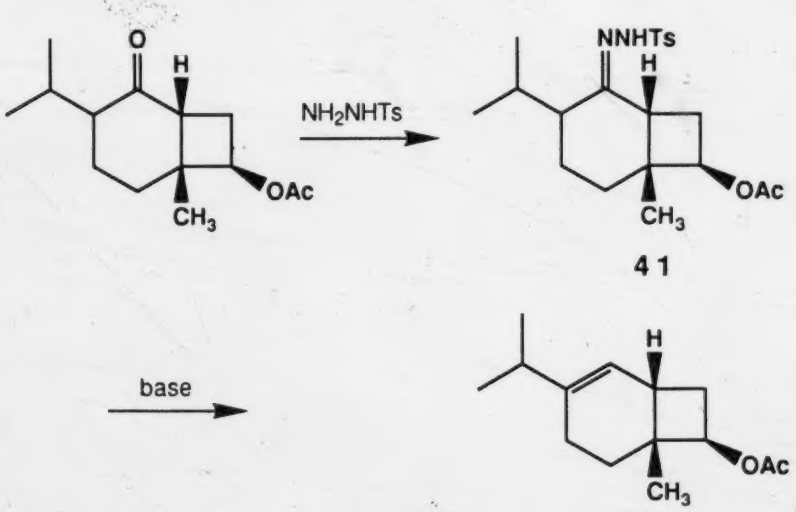
dichloromethane. The same reaction was carried out on the minor alcohol, however only a 35% yield of alkene **36** was formed. Both alcohols from isomer II of acetate **38** were also dehydrated in dismal yields (20 to 25%), however all four alcohols formed the same alkene, substantiating that the stereochemistry around the acetate unit was the same for isomers I and II. Alkene **36** no longer showed an O-H band in the infrared spectrum, but still gave a strong carbonyl stretch at 1739 cm^{-1} for the acetate unit. An olefinic proton could be seen in the ^1H NMR spectrum at δ 5.44 as a broad singlet. The isopropyl group coalesced into a doublet at δ 0.96 instead of showing as its usual pair of doublets and the allylic methylene protons could be easily distinguished (δ 1.9 and 1.66) as each showing a ddd with a geminal coupling of 13.5 Hz.

In an attempt to efficiently utilize all the alcohols, the reduction products from isomer II were reacted with copper sulphate on silica gel,[33] a method of dehydration which was also found to be effective on the major alcohol from isomer I of acetate **38**. The copper sulphate catalyst had the advantage over most commonly used metal catalysts in that lower temperatures (refluxing toluene) could be used and workup involved merely a filtration. Unfortunately, after refluxing overnight, only starting material was present in each case.

The inability of the minor alcohol from isomer I and the two alcohols from isomer II to eliminate cleanly suggested they had the incorrect orientation for this type of dehydration (ie. *cis*- or di-equatorial orientation of the proton and the hydroxyl group). Therefore, an alternative method for forming the alkene which did not involve a dehydration step was investigated.

The Bamford-Stephens reaction has been known since 1967. It involves the decomposition of *p*-toluenesulfonylhydrazones by a strong base to directly form an alkene (see Equation 5). With this in mind, the tosylhydrazones of isomers I and II of acetate **38** were formed.

Reaction of isomer I with 1.2 equivalents of tosylhydrazine in refluxing methanol produced a mixture of two tosylhydrazones **41** in 50% yield based on recovered starting material. Isomer II produced the same two compounds in 82% yield under the same conditions suggesting epimerization of the isopropyl group was occurring. Again, 20-30% starting material was recovered, even after long reaction times and the use of 2 equivalents of hydrazine. Presumably the steric bulk of the isopropyl group hindered the reaction. By the addition of magnesium sulfate, the reaction could be pushed to completion and the tosyl hydrazones from isomer I could be formed in ~70% yield.



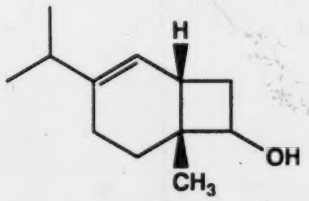
Eq. 5

Confirmation of the structure came from the following spectral data. Hydrazone I showed a stretch at 3180 cm^{-1} for the N-H bond in the infrared spectrum along with a band for the acetate carbonyl at 1735 cm^{-1}. The ^1H NMR spectrum showed the presence of the aromatic peaks at δ 7.25 and 7.85, as well as a singlet at δ 2.0 for the aromatic methyl group. HRMS showed a molecular ion peak at 406.1943 corresponding to the desired formula $C_{21}H_{30}N_2O_4S$. Similar data was seen for hydrazone II.

For the elimination, a non-nucleophilic base was required in order to keep the acetate group intact, thus eliminating commonly used bases such as methoxide and ethoxide ion. Also, as conditions had to be capable of being scaled up, bases such as *n*-BuLi were avoided. Sodium hydride became the reagent of choice.

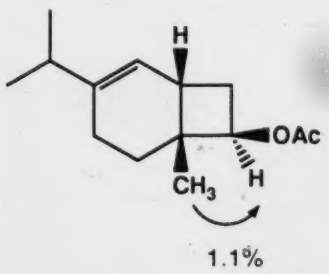
Hydrazone I was refluxed with 2 equivalents of sodium hydride in DMF for 1.5 hours, generating an 80% yield of the alkene. Similarily, the second tosylhydrazone was eliminated in 76% yield after 3.5 hours, with some hydrolysis of the product in the process. The hydrolyzed product **42** could be reacetylated using acetic anhydride in pyridine. Isomers III and IV of acetate **38** could be also transformed into their corresponding alkene **43** *via* formation of the tosylhydrazones and subsequent elimination in about 50% overall yield.

The stereochemistry surrounding the acetate group was reconfirmed at this stage by carrying out NOE studies on the alkene acetates generated from both sets of the photoadducts. Upon irradiation of the ring junction methyl group of both isomers, the alkene acetate from photoadducts I and



42

II showed a smaller NOE to the hydrogen adjacent to the acetate group than the isomer from photoadducts III and IV (1.1% versus 2.9%). This confirmed that the acetate and methyl group were *cis* in the major isomers and *trans* in the minor ones.



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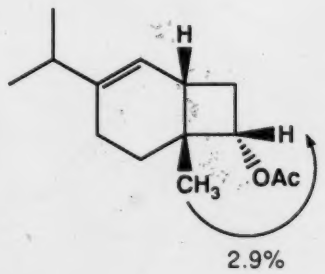
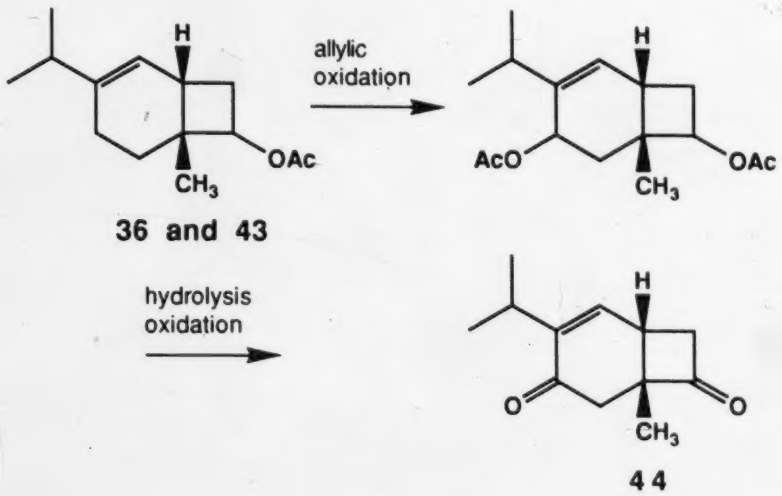


43

With the alkenes **36** and **43** in hand, the next stage of the synthesis required a selective oxidation at the allylic methylene position, thus preparing the A ring for the Michael addition of a vinyl group. Several methods are available in the literature, most using selenium or chromium reagents. Different oxidation conditions allow for the introduction of various groups to the allylic position, for example hydroxyl or acetate units. Initially, the idea of introducing an acetate group was appealing as both

acetates could then be removed and the hydroxyl groups simultaneously oxidized to form the enone **44** (see Equation 6).

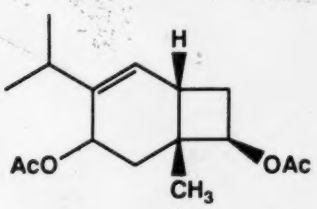


Eq. 6

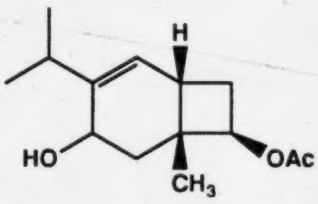
With this in mind, alkene **36** was reacted with selenium dioxide in glacial acetic acid at refluxing temperatures.[34] Two compounds were formed, the desired acetate **45** in 23% yield and alcohol **46** in 18% yield. The diacetate showed a strong carbonyl band in the infrared spectrum at 1735 cm^{-1}. The ^1H NMR spectrum showed signals at δ 5.71 (m, 1H) and 5.41 (m, 2H) for the olefinic proton and those adjacent to the acetate units. Two methyl signals for the acetate units were visible at δ 2.14 and 2.18 as singlets. Mass spectroscopy confirmed the formula $C_{16}H_{24}O_4$ with a peak at 280.1679.

The allylic alcohol **46** showed a broad signal in the infrared spectrum centered around 3440 cm^{-1}, along with a stretch at 1738 cm^{-1} for the

acetate group. Three downfield peaks were evident in the ^1H NMR spectrum, one at δ 5.50 for the olefinic proton, one at δ 4.78 for the proton adjacent to the acetate group and the third at δ 4.52 for the proton next to the hydroxyl group. Again, mass spectroscopy confirmed the formula $C_{14}H_{22}O_3$ with a peak at 238.1566.



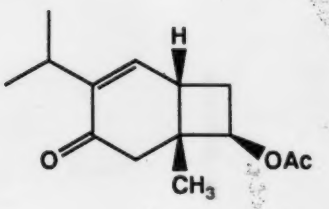
45



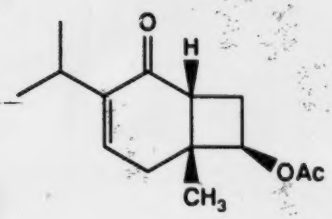
46

The low yield led us to consider other methods of oxidation. Several methods using chromium reagents have been reported. PCC was found to have no effect on our molecule,[35] and sodium dichromate oxidation[36] formed an inseparable mixture (in low yield) of enones **47** and **48**. An explanation for the formation of product **48** would be through rearrangement of the allylic radical which is formed during the reaction. Alternatively, the chromium ester intermediate could undergo a 1,3-oxygen transposition. For this reason, chromium based reagents were avoided for the allylic oxidation.

Sharpless developed a method of oxidation which used catalytic amounts of selenium dioxide with *tert*-butylhydroperoxide to re-oxidize the selenium back to SeO_2.[37] This method was tried and a mixture of the allylic alcohol **46** and the enone **47** was isolated, along with starting material and some

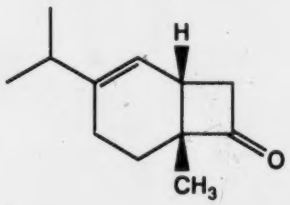


47



48

over-oxidized compound. Again, the yield was low; however, oxidation of the allylic alcohol with PDC was carried out to generate more of the enone system. Unfortunately, PDC also caused some rearrangement to occur forming an inseparable mixture of enone acetates. At this point we decided to prepare the keto-alkene **49** to see if a different system would produce better results.



49

Alkene acetate **36** was easily hydrolyzed in 95% yield using potassium carbonate in aqueous methanol. The infrared spectrum showed a broad O-H stretch at 3320 cm^{-1} and the carbonyl stretch from the acetate unit was noticeably absent. The ^1H NMR spectrum showed a shift for the proton that was adjacent to the acetate group from δ 4.89 to 4.10 and gave no trace of the acetate methyl group. High resolution mass spectroscopy showed a molecular ion peak at 180.1505 for the formula $C_{12}H_{20}O$.

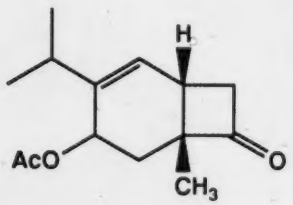
Swern oxidation[38] generated the four-membered ring ketone in nearly quantitative yield, as shown by the distinctive carbonyl stretch in the infrared spectrum at 1779 cm^{-1}. The methylene protons on the cyclobutane ring were also affected, their geminal coupling constant increased from 11 Hz in the alkene acetate to 17.5 Hz for the cyclobutanone system, which is typical for geminal protons adjacent to an sp^2 center. Again, mass spectroscopy confirmed the structure with a molecular ion peak at 178.1359 for the formula $C_{12}H_{18}O$.

Using selenium dioxide in glacial acetic acid, an allylic acetate unit could be introduced into the newly formed keto-alkene to generate compounds **50** with yields ranging from 25 to 45%. The ^1H NMR spectrum showed there to be an inseparable mixture of two acetates formed in a 2:1 ratio. The major isomer showed an olefinic proton at δ 6.0 as a doublet and a triplet at δ 5.38 for the proton adjacent to the acetate unit. The methyl signal for the acetate unit showed at δ 1.96 as a sharp singlet. The two geminal protons on the A ring came at δ 2.32 and 1.42, each as a doublet of doublets showing a geminal coupling constant of 13 Hz. The methylene protons on the cyclobutanone ring were also visible, each showing as a doublet of doublets at δ 3.36 and at δ 2.80, with a geminal coupling constant of 18 Hz. Infrared spectroscopy gave two carbonyl stretches, one at 1781 cm^{-1} for the cyclobutane ketone and the second at 1736 cm^{-1} for the acetate unit. Mass spectroscopy gave a molecular ion peak at 236.1410 for the molecular formula $C_{14}H_{20}O_3$.

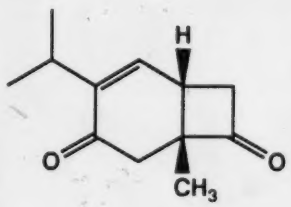
Before trying to improve upon this yield, the enone system **44** was generated to determine if 1,4-addition of a vinyl group could be selectively

carried out in the presence of the unprotected four-membered ring carbonyl. This required two steps, hydrolysis of the acetate unit and oxidation to the enone.

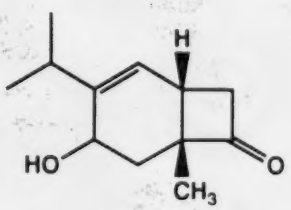
Potassium carbonate hydrolysis in aqueous methanol cleanly formed compound **51**. However, column chromatography decomposed some of the sensitive allylic alcohol, giving only a 65% yield. Very little of the minor alcohol came off the column and it was impure, suggesting that it may have been preferentially decomposed on the column. The major alcohol showed a broad O-H band at 3450 cm^{-1} in the infrared spectrum and the acetate carbonyl had disappeared. The ^1H NMR spectrum showed an upfield shift for the proton adjacent to the hydroxy group, from δ 5.38 for the acetate to δ 4.32 for the alcohol. Again, HRMS showed the molecular ion peak at 194.1299 for the desired formula $C_{12}H_{18}O_2$.



50



44



51

PDC oxidation cleanly generated the enone system **44** in nearly quantitative yield. This compound showed the typical stretch for the four-membered ring carbonyl at 1781 cm^{-1} in the infrared spectrum. A second carbonyl was evident at 1672 cm^{-1}, for the enone group. The ^1H NMR spectrum was quite simple. The olefinic proton resonated at δ 6.65

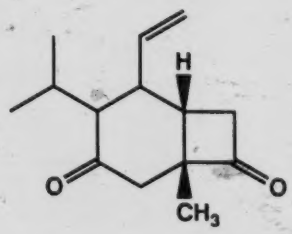
as a multiplet. The geminal protons on the cyclobutane ring appeared at δ 3.68 (dd, J = 9, 14 Hz) and 2.76 (dd, J = 4, 14 Hz) with the large geminal coupling constant of 14 Hz. The geminal protons on the cyclohexenone ring each showed as a doublet (δ 2.76 and 2.20), having a geminal coupling constant of 18 Hz. Mass spectroscopy confirmed the formula $C_{12}H_{16}O_2$ with a peak at 192.1128.

Interestingly, when both steps were run without purification inbetween, a 73% yield of an inseparable mixture (7:3 ratio) of keto-enone **44** and the rearranged system was obtained. Presumably PDC again caused some rearrangement of the allylic alcohol and as pure alcohol **51** gave no rearranged product, one can speculate that the minor alcohol was the one which rearranged. The newly formed compound was also found to be somewhat volatile, causing some difficulties in handling.

Before trying other methods of oxidation to avoid the rearrangement problem, selective addition of copper mediated vinylmagnesium bromide to the enone system was attempted to determine if this would be a viable route.

Compound **44** was reacted with 2.5 equivalents of vinylmagnesium bromide and 1 equivalent of cuprous iodide at -78°C in THF. A 60% yield of an inseparable mixture of two isomeric vinyl addition products **52** (3:1 ratio by ^{1}H NMR analysis) were obtained, along with some starting material and some bis-addition product. The infrared spectrum showed the presence of two ketones with stretches at 1781 cm^{-1} (cyclobutanone) and 1709 (cyclohexanone). The olefinic proton of the enone was replaced

with two sets of vinylic protons, integrating to 3 protons. Mass spectroscopy provided the molecular ion peak at 220.1452 for the desired formula, $C_{14}H_{20}O_2$.



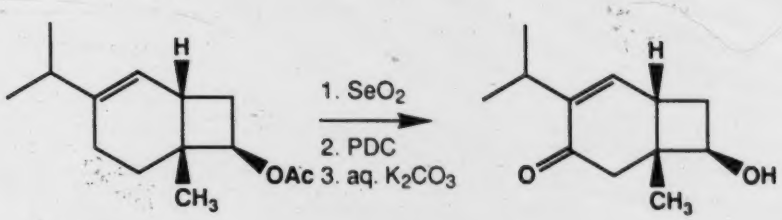
52

The volatility of the enone, the rearrangement problems of the oxidation step and the moderate selectivity of the Grignard addition prompted us to try altering our system. By protecting the cyclobutane ketone after the allylic oxidation step, the added molecular weight would hopefully solve the volatility problem and the protecting group would assist the selectivity of the Grignard addition. The problem of the rearrangement of the allylic alcohol during oxidation could probably be solved by using a different oxidation method, such as a Swern oxidation.

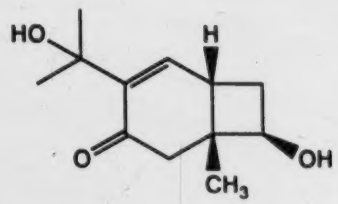
With this in mind, keto-acetate **50** was subjected to typical ketalization conditions of *p*-toluenesulfonic acid, ethylene glycol and refluxing benzene in a Dean and Stark apparatus. None of the desired product was formed, the reaction only generated a mixture of uncharacterizable aromatic compounds. Milder methods for forming the ketal, such as using lower boiling solvents or the use of trimethylsilyl choride were unsuccessful.

At this point, we decided to go back to our initial compound, alkene acetate **36**, to try one further allylic oxidation which would directly put a hydroxyl group into the allylic position. The method was a modification of a procedure used by Corey, in the synthesis of (±)-tricyclohexaprenol.[39] He utilized selenium dioxide in refluxing ethanol with 2 equivalents of pyridine present. Under these conditions, our compound was very unreactive and mainly starting material was left after refluxing overnight. By changing the solvent to xylene for a higher temperature and still adding 2 equivalents of ethanol for a proton source, a reasonably clean oxidation could be carried out, as seen by TLC. Since the allylic alcohols tended to decompose on the column and the enones were volatile, PDC oxidation to enone **47** and hydrolysis of the acetate to the alcohol **53** were carried out in succession with no intermediate purifications. Over three steps, enone-alcohol **53** could be formed in 40-45% yield, with no rearrangement of the enone system. Also isolated was 1-10% of over-oxidized material **54** (see Equation 7.

The enone system of **53** was in evidence by the carbonyl stretch in the infrared spectrum at 1669 cm^{-1}, along with a broad band at 3420 cm^{-1} signifying the presence of the O-H group. The ^1H NMR spectrum showed the olefinic proton at δ 6.54 as a doublet, a signal at δ 4.08 for the proton adjacent to the hydroxyl group, and a large coupling constant (17 Hz) for the two geminal protons on the cyclohexenone ring, indicating that they were adjacent to a carbonyl. The ^{13}C NMR spectrum showed a carbonyl peak at δ 200.4, along with two olefinic carbons at δ 143.6 and 143.5. HRMS gave a molecular ion peak at 194.1309 for the formula $C_{12}H_{18}O_2$.



36 53



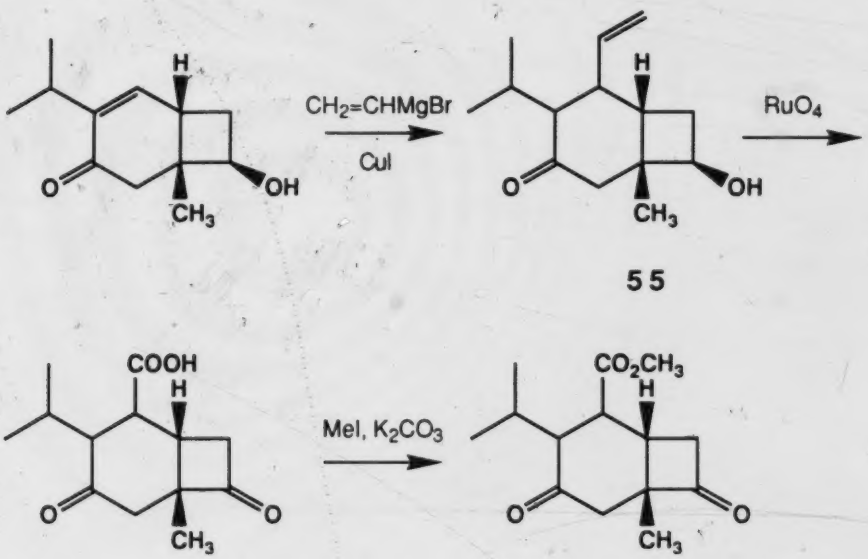
54

Eq. 7

Compound **54** showed bands in the infrared spectrum for the enone carbonyl (1655 cm^{-1}) and the hydroxyl groups (3400 cm^{-1}). The proton NMR spectrum showed a downfield shift from δ 1.03 and 0.98 to δ 1.41 and 1.39 as compared to compound **53** for the methyl groups on the isopropyl group. The mass spectrum confirmed the formula $C_{12}H_{18}O_3$ with a molecular ion peak at 210.1263.

At this point, three steps remained to bring us to the intermediate diketones **35**, which had been previously prepared by Nelson through a different route. The first step was the copper catalyzed Grignard addition of a vinyl group. The enone-alcohol had the added advantage of only having the enone system available for addition and therefore required no protection step. Secondly, oxidative cleavage of the vinyl group, hopefully

with concurrent oxidation of the hydroxyl group, and formation of the methyl ester would lead to the desired diketone, as shown in Equation 8.

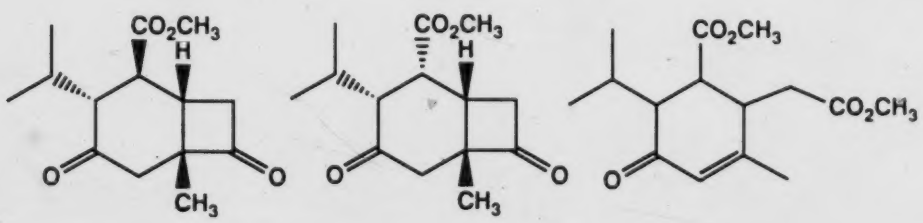


Eq. 8

The selective 1,4-addition was carried out using 6 equivalents of vinyl-magnesium bromide and 0.25 equivalents of cuprous iodide at -78°C. This formed an inseparable mixture of two isomeric compounds **55**, in 87% yield, in a 2:1 ratio as seen in the NMR spectrum. The infrared spectrum no longer showed an enone system, but gave a band typical for a 6-membered ring ketone at 1704 cm^{-1}. The ^1H NMR spectrum showed two sets of vinylic protons partially overlapping between δ 5.0 and 5.8. The protons adjacent to the hydroxyl groups could be seen at δ 4.25 for the major isomer and δ 4.10 for the minor isomer, both showing as broad quartets. The remaining protons were hard to assign due to overlap, except for the appearance of two isopropyl groups and two ring junction

methyl groups. Mass spectroscopy confirmed the formula $C_{14}H_{22}O_2$ with a peak at 222.1618.

The resultant vinylic compounds could be oxidized to the diketo-acids by the Sharpless method,[40] using a catalytic amount of ruthenium trichloride and excess sodium metaperiodate to generate ruthenium tetroxide *in situ*. This was found to be the most successful method for forming ruthenium tetroxide, which was a desirable reagent for us as it was known to oxidize alcohols to ketones. For ease of workup, the newly formed carboxylic acids were directly esterified with methyl iodide and potassium carbonate. After these two steps, a 60% yield of two diketones, **56** and **57**, were generated in a 3:1 ratio.

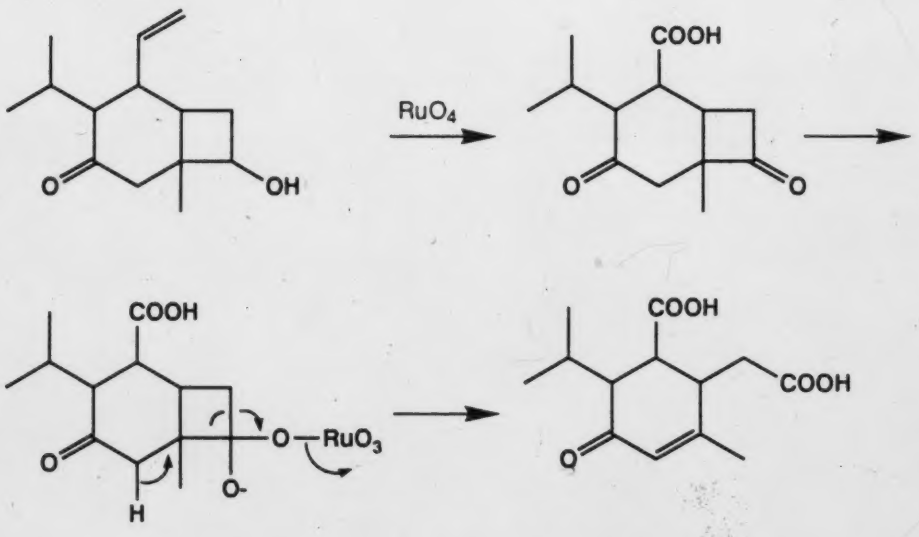


56 **57** **58**

The major isomer **56** exhibited three carbonyl stretches in the infrared spectrum, 1784 cm^{-1} for the cyclobutane ketone, 1736 cm^{-1} for the ester and 1713 cm^{-1} for the ketone in the cyclohexane ring. All traces of vinylic protons had disappeared from the ^1H NMR spectrum and a sharp singlet was in evidence at δ 3.75 for the methyl ester. Two sets of methylene protons could be seen, the set adjacent to the ketone in the A ring showing as a pair of doublets with a geminal coupling of 14 Hz, and the set on the

cyclobutane ring showing as a pair of doublets of doublets with a geminal coupling constant of 18 Hz. The ^{13}C NMR spectrum showed there to be three carbonyls in the molecule, two ketones (δ 209.7, 208.9) and one ester (δ 173.6). HRMS gave the molecular ion peak at 252.1367 for the formula $C_{14}H_{20}O_4$. The second isomer showed similar data.

Also isolated from the reaction mixture was ~10% of compound **58**. Formation of this by-product could conceivably be through attack of the newly formed cyclobutane ketone by another molecule of ruthenium tetroxide and subsequent Grob-type fragmentation, as shown in Equation 9.



Eq. 9

Support for this structure was seen in the infrared spectrum by the presence of both ester and enone carbonyl stretches at 1738 and

1668 cm^{-1}, respectivily. The ^1H NMR spectrum showed two singlets for the methyl esters, at δ 3.17 and 3.14, along with an olefinic proton at δ 5.88. The methyl group on the six membered ring was shifted downfield to δ 1.94, suggesting it resided on a double bond instead of at a ring junction. HRMS confirmed the formula $C_{15}H_{22}O_5$ with a peak at 282.1460.

The stereochemistry around the isopropyl and ester groups of the two new diketones could be determined from the coupling constants of the adjacent hydrogens. For the major isomer **56**, the ring junction hydrogen (position 6 on the ring) resonated at δ 2.92 as a ddd with coupling constants of 4, 9, and 12 Hz. The methylene protons on the cyclobutanone ring showed coupling constants of 4 and 9 Hz, respectively to the ring junction proton, leaving the 12 Hz coupling to the proton adjacent to the ester group (in the 5 position on the ring). This proton resonated at δ 2.92 as a triplet with a coupling constant of 12 Hz, suggesting a *trans* diaxial relationship between the protons at positions 5 and 6 as well as between 4 and 5 on the six membered ring.

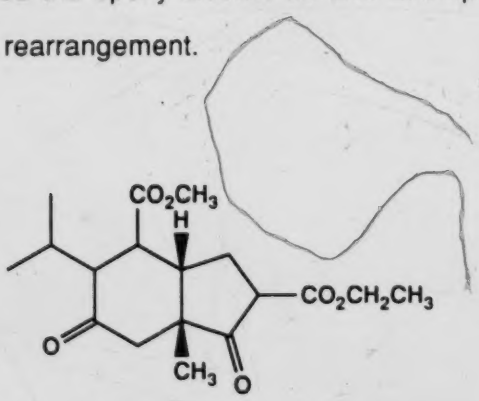
Conversely, in isomer **57** the proton adjacent to the ester group (δ 3.24, dd) showed coupling constants of 3 and 4 Hz towards the neighbouring protons, showing the three protons to have an all *cis* relationship.

A further proof that these two compounds were isomeric came from epimerization of the all *cis* isomer to the more stable isomer **56**. Reaction of pure isomer **57** with 1 equivalent of potassium carbonate in methanol at

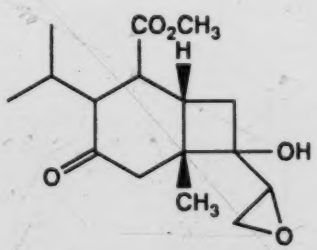
room temperature quickly formed the same 75:25 ratio of the isomers in quantitative yield.

Neither of the two isomers had the stereochemistry around the isopropyl group which was required for dendrobine. However, the carbonyl group adjacent to that center was a handle for epimerization at a later stage in the synthesis.

With the diketone **56** in hand, we were able to pursue the ring expansion step. Several methods have been developed over the years, such as pinacolic-type rearrangements, the Tiffeneau-Demjanov rearrangement, spiroannelation methodology, and the use of diazomethane.[41,42] The initially planned method of using ethyl diazoacetate to form the keto-ester **59** was studied by Nelson and found to be unsuccessful. Nelson also formed the epoxy-alcohol **60** and attempted an acid catalyzed pinacolic-type rearrangement.

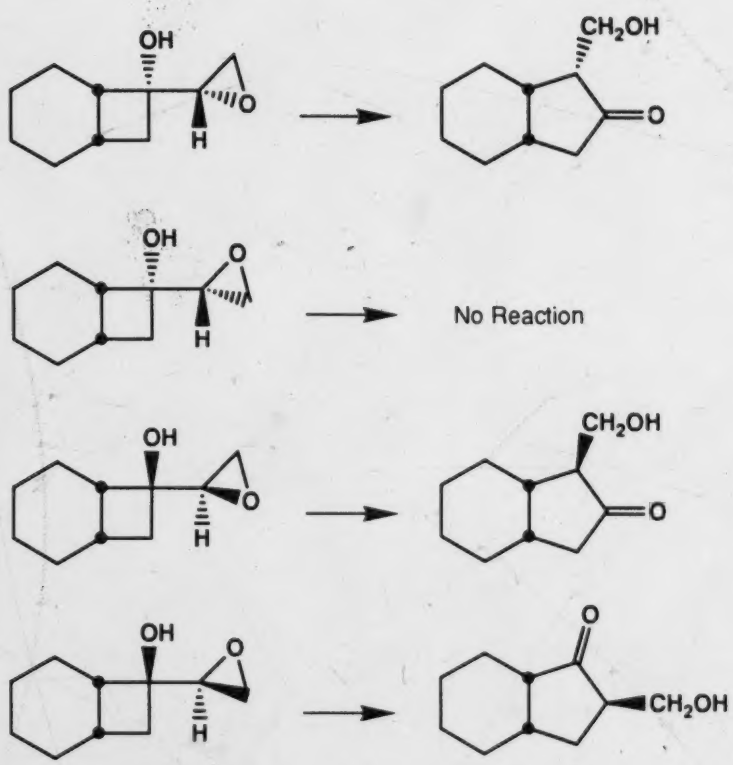


59



60

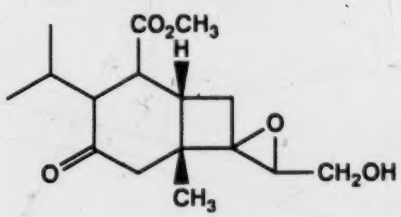
SCHEME 10



This type of ring expansion has been published previously by Reusch on the bicyclo[4.2.0]octanol ring system seen in Scheme 10.[43,44] Four different diastereomers were studied, three of which rearranged to the hydroxymethyl ketones under boron trifluoride etherate conditions.

Nelson formed the epoxy alcohols, but found no evidence of ring expansion products under a number of Lewis acid conditions. However,

he did isolate one interesting compound from a reaction with stannic chloride, tentatively given the structure **61**.



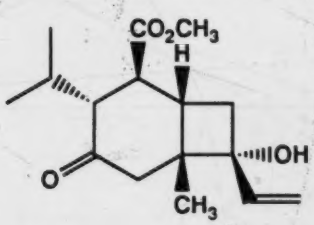
61

As it was well documented that spiro epoxides undergo ring expansion using lithium iodide,[45] we set out to prepare this interesting and hopefully useful compound.

Using the major diketone **56** we carried out a selective addition of vinyllithium to the cyclobutanone group. Thus, 1.2 equivalents of vinyllithium was added to a -78°C THF solution of the diketone, forming the desired vinyl alcohol **62**. Typically, yields ranged from 65-75%, with varying amounts of starting material and bis-addition products also being formed. Only one isomer was produced, with addition presumably coming from the less hindered convex face of the molecule. Infrared spectroscopy showed the cyclobutane ketone to no longer be present. However, the ester (1736 cm^{-1}) and the cyclohexanone group (1712 cm^{-1}) were still intact. As well, a large O-H stretch was apparent at 3450 cm^{-1}. The three vinylic protons were easily distinguished in the proton NMR spectrum, coming at δ 6.02 (dd, J = 10, 17 Hz), 5.45 (dd, J = 1, 17 Hz), and 5.36 (dd, J = 10, 1 Hz). The coupling constant for the geminal protons on the

cyclobutane ring also dropped to 13.5 Hz, suggesting they were no longer adjacent to an sp^2 center. Chemical ionization mass spectroscopy showed an $(M+NH_4)^+$ peak at 298.3148.

Epoxidation could be easily carried out using MCPBA in dichloromethane at room temperature for four hours. Two epoxides **63** were formed in a 1.6:1 ratio in 90% yield. In both cases the vinylic protons were no longer evident in the ^1H NMR spectrum. The major epoxide showed peaks at δ 3.38 (dd, J = 2.5, 4 Hz), 2.90 (dd, J = 2.5, 5 Hz), 2.79 (dd, J = 4, 5 Hz) for the protons on the oxirane ring. Mass spectroscopy gave a molecular ion peak at 296.1611 for the formula $C_{16}H_{24}O_5$.



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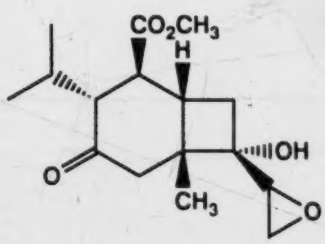
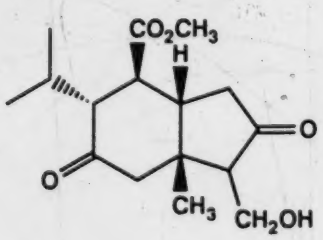


63

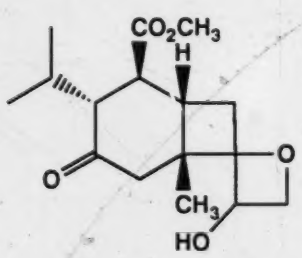
The major epoxide was reacted with stannic chloride at 0°C in dichloromethane for 30 minutes. A new compound was formed in nearly quantitative yield, showing all the characteristic peaks for the A ring in the ^1H NMR spectrum, but being distinctively different for the remaining part of the molecule. Infrared spectroscopy showed an O-H stretch at 3470 cm^{-1}, an ester carbonyl at 1733 cm^{-1} and the cyclohexane ketone at 1713 cm^{-1}. A doublet of doublets at δ 3.98 (J = 3, 9 Hz) indicated the presence of one proton adjacent to a hydroxyl group. It was coupled to two protons which

resonated at δ 3.64 as an over'apping pair of doublets of doublets with coupling constants of J = 3, 11 Hz for one and J = 9, 11 Hz for the other. This was contrary to both the tentative structure **61** or the ring expansion product **64**, both of which would have a primary hydroxyl group, not a secondary one. The second epoxy alcohol also formed a similar compound under the same reaction conditions. Acetylation of the compound derived from the major epoxide **63** caused a downfield shift in the proton at δ 3.64 to 5.3, indicating that indeed, only one proton was adjacent to the O-H group.

The product from the acid catalyzed rearrangement was assigned structure **65** based on the proton NMR spectrum. In an attempt to prove the existance of the cyclobutanol ring, PCC oxidation was carried out to form a cyclobutane ketone, which would then show a distinctive stretch at ~1780 cm^{-1} in the infrared spectrum. Therefore compound **65** (formed from the minor epoxide) was dissolved in hexanes and reacted with excess PCC on alumina. Interestingly, the only product isolated from the reaction mixture was the diketone **56**, albeit in low yield. The formation of this product did show that the B ring was still intact in compound **65**.

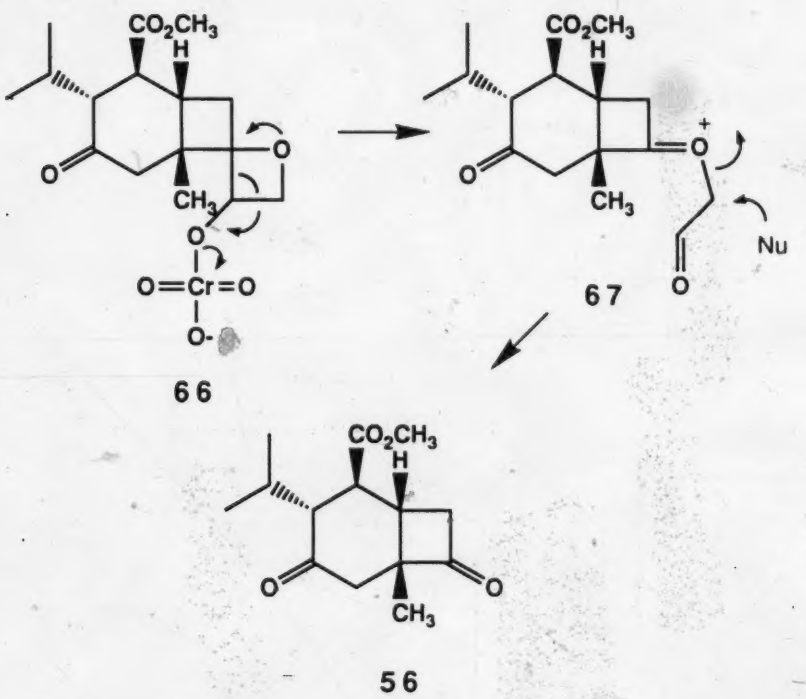


64



65

Assuming that our structure for **65** is correct, a reasonable mechanism for the formation of the diketone is as follows. Decomposition of the chromium ester **66** previous to oxidation would form the reactive intermediate **67**, which through attack by any nucleophile would generate the diketone **56** as shown in Equation 10.

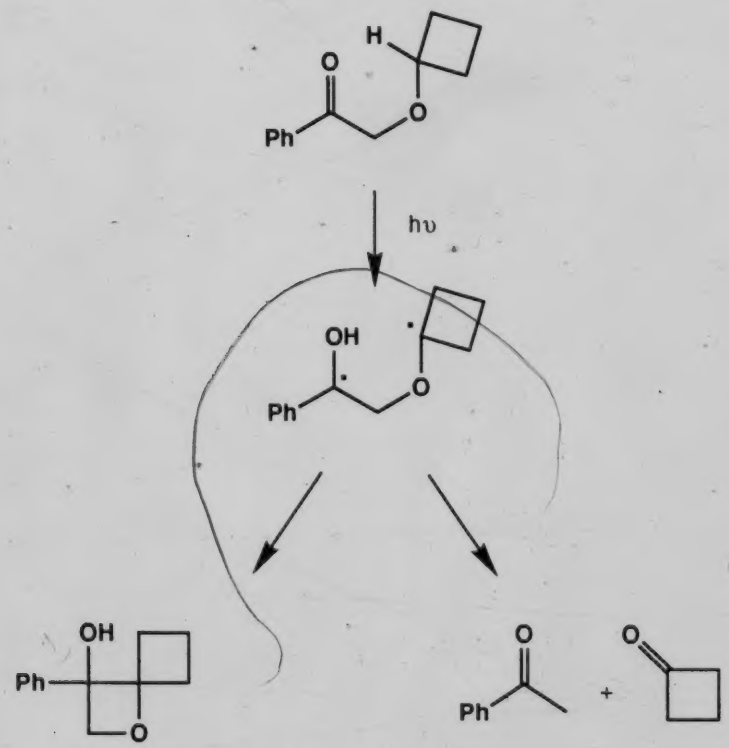


Eq. 10

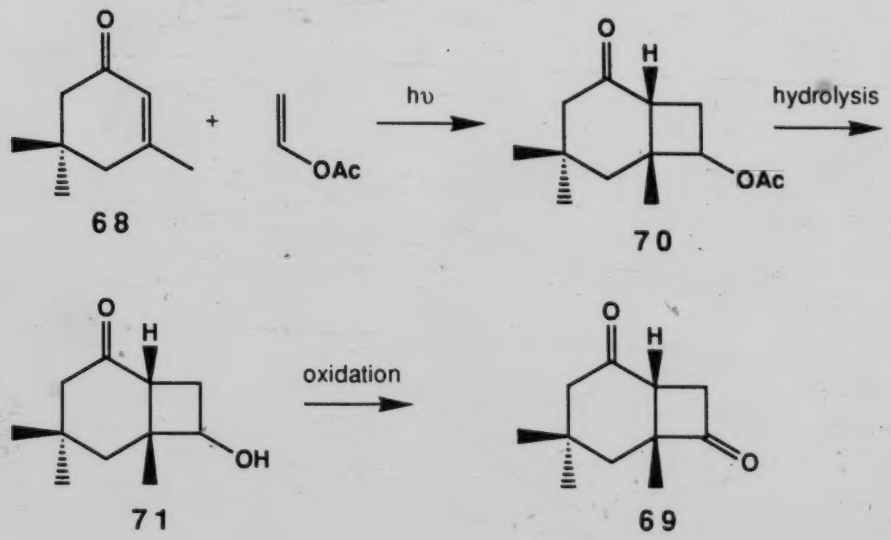
Very little information is available on the class of compounds known as 3-hydroxy-1-oxaspiro[3.3]octanes, however they have been formed before through the photolysis of α-cycloalkoxyacetophenones (see Scheme 11).[46]

The ring expansion step was obviously not going to be an easy process, therefore we decided to develop a model compound for further studies. This would also give us the opportunity to study the rearrangement reaction of the epoxy alcohol on a larger scale. In choosing our model compound, we wanted to include a methyl group at the ring juncture and also have some functionalities on the A ring in order to mimic our own system as closely as possible. A suitable candidate for the photocycloaddition was isophorone **68** as it was known to undergo the photoreaction readily and it seemed to fit all our requirements. We set out

SCHEME 11



to form diketone **69** through a photocycloaddition reaction with vinyl acetate, hydrolysis of the product and oxidation of the resultant alcohol to the cyclobutanone ring (see Equation 11).



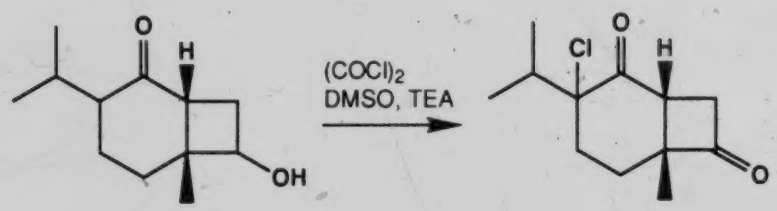
Eq. 11

The photocycloaddition was carried out under the same conditions as for piperitone and vinyl acetate. After treatment with DBU, two isomeric compounds **70** were formed with a 60% yield of isomer I and 18% yield of isomer II, along with the recovery of 10% of the starting material. The relative stereochemistry of the two isomers was not determined as the chiral center around the acetate unit was going to be destroyed. Isomer I showed two carbonyl stretches in the infrared spectrum, one at 1740 cm^{-1} for the acetate unit and the other at 1708 cm^{-1} for the ketone. The proton adjacent to the acetate group resonated at δ 4.92 in the ^1H NMR spectrum, and four methyl signals could be discerned. HRMS did not

show the molecular ion peak, however it did show a peak for loss of acetate.

Isomer I of acetate **70** was easily hydrolyzed to the alcohol **71** in 72% yield using potassium carbonate in refluxing aqueous methanol. The product showed a broad O-H band centered around 3420 cm^{-1} in the infrared spectrum, with the acetate carbonyl no longer present. The proton adjacent to the hydroxyl group was shifted upfield to δ 4.10. Mass spectroscopy confirmed the formula $C_{11}H_{18}O_2$ with a signal at 182.1310.

All that remained to form our model compound was oxidation of the cyclobutanol group. This was carried out using a procedure developed in our laboratories by Nyangulu. He utilized phenyl dichlorophosphate (PDCP) as the activating group in a modification of the Swern oxidation.[25] The modified Swern was used as previous work in our group had shown that Swern oxidation of a cyclobutanol in the presence of another ketone can cause chlorination α to the keto group (see Equation 12).



Eq. 12

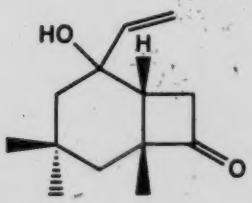
Thus, to a solution of 5 equivalents of DMSO in dichloromethane at -10°C were added sequentially 3 equivalents of PDCP, 5 equivalents of

triethylamine and then alcohol **71**. After slowly warming to room temperature and then working up, a 72% yield of the desired diketone **69** was formed. Infrared spectroscopy showed the distinctive stretch for the cyclobutanone unit at 1782 cm^{-1} along with the six-membered ring ketone at 1709 cm^{-1}. The methylene protons on the four-membered ring each showed as a doublet of doublets (δ 3.20, J = 5, 18 Hz and δ 3.52, J = 11, 18 Hz) with the large geminal coupling constant of 18 Hz. Again, the formula $C_{11}H_{16}O_2$ was confirmed by a molecular ion peak at 180.1149 in the HRMS.

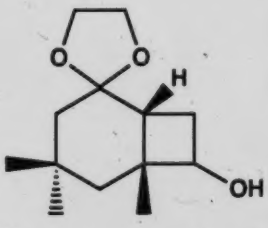
At this stage we wanted to repeat the epoxide rearrangement reaction on the model compound to see if the unusual rearrangement product was a general occurrence. The next step involved the selective addition of vinyllithium to the more reactive four-membered ring ketone. As selectivity was seen between the two carbonyls in the real system, we hoped to obtain the desired vinyl alcohol in this case as well. However, the only product which could be isolated from the reaction mixture was vinyl alcohol **72**, in only 30% yield. Apparently, vinyllithium added preferentially to the six-membered ring ketone. The infrared spectrum still showed the cyclobutanone carbonyl to be present with a stretch at 1771 cm^{-1}. The three vinylic protons were visible in the ^1H NMR spectrum, showing at δ 6.04, 5.30 and 5.14.

The reversed selectivity for the Grignard addition could be explained by comparison of the steric hinderance surrounding the ketone in the A ring of both compounds **56** and **69.** In diketone **56**, the isopropyl group impedes the addition because of its proximity and bulk. Conversely, the

cyclohexanone group in model compound **69** is actually less hindered than the cyclobutane ketone and is therefore preferentially attacked.



72



73

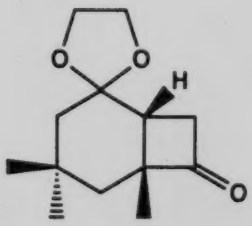
Solving this problem was a simple matter of protecting the A ring carbonyl previous to the formation of the four-membered ring ketone. Therefore, keto-alcohol **71** was ketalized using *p*-toluenesulfonic acid and ethylene glycol in refluxing benzene. Ketal **73** was formed in 80% yield, as seen by the disappearance of the carbonyl stretch in the infrared spectrum and the appearance of the ketalic protons as a multiplet at δ 3.85 in the ^{1}H NMR spectrum.

Oxidation of the alcohol to ketone **74** was accomplished with a Swern oxidation in 85% yield, with the cyclobutanone ring in evidence from the carbonyl stretch in the infrared spectrum at 1778 cm^{-1}.

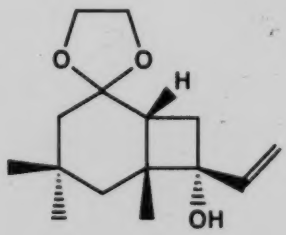
All that was required now was formation of the vinyl alcohol and epoxidation to the epoxy-alcohol which could then be used to test the acid catalyzed rearrangement.

Addition of vinyllithium was carried out at -78°C in THF. One vinylic alcohol **75** was formed in 78% yield, presumably *via* addition to the least hindered convex face of the molecule. A broad O-H stretch centered around 3580 cm^{-1} was visible in the infrared spectrum. The vinylic protons resonated at δ 5.18 (dd, J = 1, 10), 5.32 (dd, J = 1,17), and 6.08 (dd, J = 10, 17). The molecular ion peak could be seen in the high resolution mass spectrum at 238.1524 for the formula $C_{13}H_{22}O_3$.

Epoxidation was carried out in 83% yield using MCPBA in dichloromethane. An inseparable mixture of two epoxides **76** was formed in approximately a 2:1 ratio. The vinylic protons present in the ^1H NMR spectrum of the starting material were replaced with a series of peaks between δ 2.8 and 3.95 for the protons on the oxirane rings. Infrared spectroscopy still showed the presence of the O-H group and mass spectroscopy confirmed the formula $C_{15}H_{24}O_4$ with a peak at 268.1679.



74

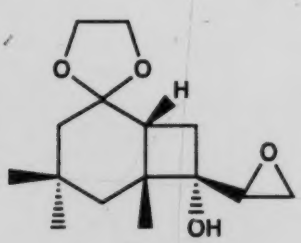


75

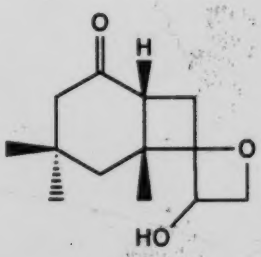
The acid catalyzed rearrangement was carried out on the mixture of epoxides and a product **77** similar to **65** was formed in low yield. The infrared spectrum showed a carbonyl stretch for the deprotected ketone at 1676 cm^{-1}, which seemed unusually low; however, the carbonyl was

confirmed by the presence of a peak in the ^{13}C NMR spectrum at δ 214. The proton NMR spectrum showed a triplet at δ 4.0 for the proton adjacent to the hydroxyl group and signals at δ 3.64 and 3.58 for the methylene protons to which it was coupled. ^{13}C NMR APT spectrum showed 8 carbons in phase and 5 carbons anti-phase to the chloroform peak, which fit the proposed structure. HRMS gave a molecular ion peak at 224.1391 for the formula $C_{13}H_{20}O_3$.

As the acid catalyzed reaction was not forming the ring expansion product, other methods for the ring expansion were investigated on the model system.



76



77

While we had the epoxy-alcohol in hand, an attempt was made at a base-catalyzed rearrangement. Deprotonation of the hydroxyl group would possibly provide an added driving force for the ring to expand. The inseparable epoxy-alcohols **76** were dissolved in THF at 0°C with 2 equivalents of sodium hydride. After warming to room temperature and stirring for 7 hours, two compounds could be isolated. One of the isomers of the starting epoxide was recovered with the second compound being

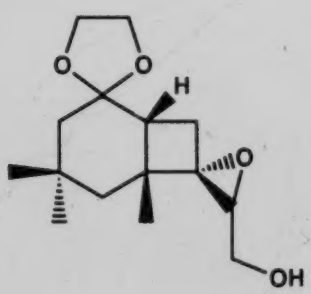
the spiro epoxide **78**. Apparently, only one of the epoxy-alcohols was able to rearrange to the spiro system under these conditions. The new compound showed a broad O-H stretch in the infrared spectrum at 3430 cm^{-1}, along with a strong C-O band at 1092 cm^{-1}. The ^1H NMR spectrum showed a peak at δ 3.58 (dd, J = 6, 12 Hz) for the proton on the epoxide ring which was coupled to a proton at δ 3.20 (dd, J = 6, 3.5 Hz) as well as to a proton hidden under the ketal resonance at δ 3.9. HRMS confirmed the formula $C_{15}H_{24}O_4$ with a peak at 268.1663.

The formation of the spiro epoxide opened up a new avenue for the ring expansion process. In 1978 Trost and Latimer utilized a method of ring expansion through rearrangement of a spiro epoxide with lithium iodide, in a synthetic approach to the gibberellins.[45] This method looked promising, provided a more efficient method to form the epoxide **78** could be found.

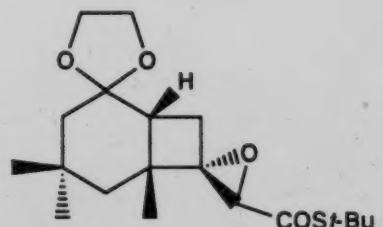
While we were working on this problem, Luo (of our laboratories) was investigating the use of thiol esters in the Darzens reaction, and their subsequent reduction to epoxy-alcohols.[47] We required an appendage on the spiro epoxide to provide a handle for forming the pyrrolidine ring after the ring expansion. The thiol ester could provide this handle as well as providing some selectivity between the two esters that would be present on the real compound if we utilized this route.

Therefore, model compound **74** was added to a -78°C solution of LDA and $BrCH_2COS$*t*-Bu. After 30 minutes the reaction was quenched and purified. A large amount of starting material was recovered (39%), along with 34% of the epoxide **79**. The structure was substantiated by the

following spectral data. A stretch at 1665 cm^{-1} in the infrared spectrum confirmed the presence of the thiol ester carbonyl. The lone proton on the oxirane ring resonated as a singlet at δ 3.55. The *tert*-butyl group showed as a singlet at δ 1.49 for nine hydrogens, while the methylene protons on the cyclobutane ring showed at δ 2.47 (dd, J = 10, 13 Hz) and 2.30 (dd, J = 9, 13 Hz). Mass spectroscopy gave a peak at 354.1861 for the formula $C_{19}H_{30}O_4S$.



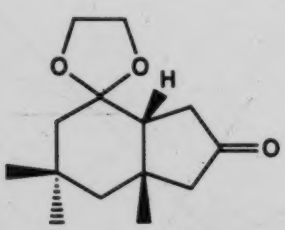
78



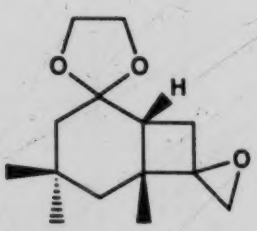
79

The newly formed epoxide was subjected to the ring expansion conditions of refluxing dioxane and lithium iodide. After 8.5 hours, a new compound was isolated in 67% yield. The thiol ester had disappeared, as evidenced by the lack of the *tert*-butyl peak in the proton NMR spectrum. There was still a carbonyl stretch in the infrared spectrum at 1742 cm^{-1}, which is typical of a 5-membered ring ketone. A new set of methylene protons were present in the ^1H NMR spectrum, one resonating at δ 1.90 (d, J = 18 Hz) and the other at δ 2.56 (d, J = 18 Hz). This information suggested that the ring had indeed expanded, but that under the conditions used the thiol ester had been removed, forming compound **80**. Lithium iodide is a

reagent which is often used for de-esterification, therefore this was an understandable product.



80



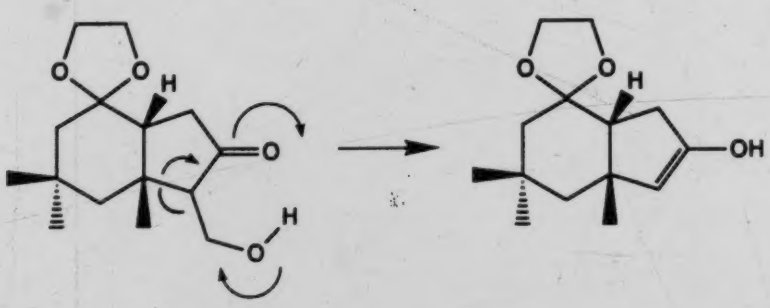
81

In order to confirm this structure, epoxide **81** was generated from ketone **74** and ring expanded. The epoxide was formed through the procedure of Corey, using trimethyl sulfonium iodide and sodium hydride in DMSO.[48] After refluxing the epoxide in dioxane with lithium iodide, an identical product to compound **80** was indeed formed.

In order to keep the appendage during the ring expansion step, the thiol ester would have to be converted into a group that could withstand the conditions being used. The thiol ester was therefore reduced to the epoxy alcohol **78** using the following procedure. Four molar equivalents of sodium borohydride were added to an ethanolic solution of compound **79**. After workup, a 75% yield of the epoxy-alcohol was formed giving spectral data identical to that for the epoxy-alcohol generated from the base catalyzed rearrangement of compound **76**.

The spiro epoxide was subjected to the ring expansion conditions and a single product was formed. Unfortunately, the hydroxy methyl group was

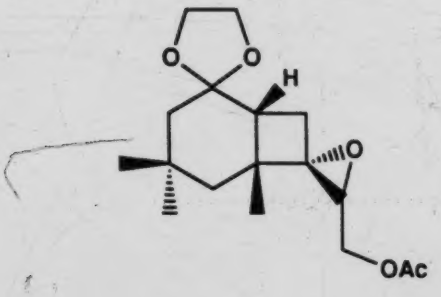
cleaved under these reaction conditions, forming compound **80**, most likely through a retro-aldol type of mechanism (see Equation 13).



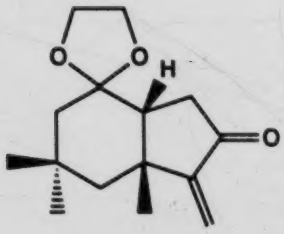
Eq. 13

In order to avoid the retro-aldol reaction, the hydroxyl group was protected with an acetate group, using acetic anhydride in pyridine. A strong carbonyl stretch in the infrared spectrum at 1745 cm^{-1} and a methyl signal at δ 2.10 in the ^1H NMR spectrum showed that the acetate **82** was formed.

Acetate **82** was refluxed with lithium iodide in dioxane and a new product was formed and assigned the structure **83** based on the following spectral data. The infrared spectrum showed a carbonyl stretch at 1727 cm^{-1}, along with a strong carbon-carbon double bond stretch at 1634 cm^{-1}. An exocyclic double bond was evidenced by two singlets at δ 5.96 and 5.16 in the ^1H NMR spectrum. The methylene protons on the five-membered ring showed as doublets of doublets (δ 2.45 and 2.34) with a geminal coupling constant of 18 Hz. Mass spectroscopy confirmed the formula $C_{15}H_{22}O_3$ with a peak at 250.1568.



82



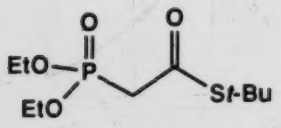
83

Having finally obtained the ring expansion product, we set out to improve upon the spiro epoxide formation. Unfortunately, the modified Darzens reaction never produced more than a 30% yield of the desired product. It was also found to be completely unsuccessful on compound **56**. Therefore, we decided to investigate the use of a thiol ester Wittig reagent to form the α,β-unsaturated thiol ester, with the idea of forming the epoxide from that intermediate.

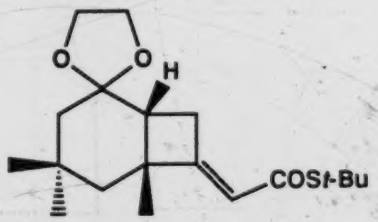
A search of the literature showed several Wittig reagents based on thiol esters had been developed, however none of them had been shown to react with ketones. For this reason, we decided to develop the more reactive Wadsworth-Emmons type reagent **84**. The discussion on the formation and reactivity of this reagent is contained in the second chapter of this thesis.

Reaction of the newly formed Emmons reagent with the model compound **74** was carried out using 1.2 equivalents of reagent **84** and one equivalent of sodium hydride in DME. The desired product **85** was formed

in 51% yield. The low yield could be due to the difficulty of forming an sp^2 center on the cyclobutane ring due to torsional strain.



84



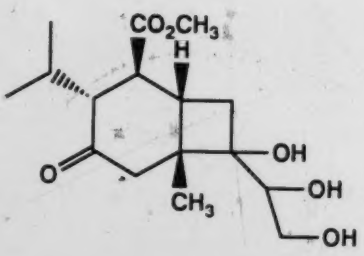
85

The compound showed a strong carbonyl stretch at 1676 cm^{-1} and a stretch for the carbon-carbon double bond at 1638 cm^{-1} in the infrared spectrum. The olefinic proton showed at δ 5.85 as a triplet, with a long range coupling constant of 2 Hz. The methylene protons on the cyclobutane ring each showed as a doublet of doublets of doublets (δ 2.98, J = 2, 8, 18 Hz and δ 3.22, J = 2, 9, 18 Hz). Both displayed coupling constants to the olefinic proton of 2 Hz and showed a strong geminal coupling of 18 Hz. The *tert*-butyl group was in evidence from a strong peak at δ 1.50.

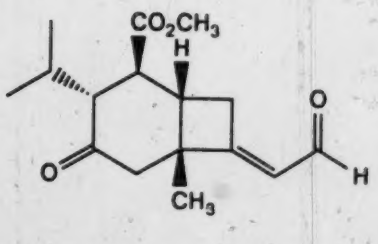
The α,β-unsaturated thiol esters were, unfortunately, not useful in the synthesis as neither the epoxide nor the allylic alcohol could be generated from them. Under epoxidation conditions with MCPBA, a streak of compounds was seen on the TLC plate, possibly through oxidation of the sulfur group. Reduction to the allylic alcohol was also unsuccessful as reducing agents which were mild enough to generate the allylic alcohol (i.e. $NaBH_4$) also produced the transesterified product. Stronger reducing

agents tended to form the saturated alcohol. As a consequence of these results we abandonded the idea of utilizing a thiol ester group to assist in the formation of the spiro epoxide and started investigating other methods to form the spiro system. The base catalyzed rearrangement of the epoxy-alcohol **76** to the spiro system **78** was a route that had been partially successful in the model compound, therefore we decided to try this on compound **63**. This was in hopes of forming the spiro epoxide, which could then be acetylated and ring expanded.

Compound **63** was treated with sodium hydride in THF. Several compounds were formed, one of which appeared to be from ring opening of the epoxide to the triol **86**. The infrared spectrum displayed a broad O-H band at 3440 cm^{-1}, along with two carbonyl stretches at 1733 cm^{-1} for the ester and 1708 cm^{-1} for the ketone. A multiplet appeared at δ 3.65 in the ^1H NMR spectrum for the proton adjacent to the secondary alcohol. Chemical ionization mass spectroscopy confirmed the formula $C_{16}H_{26}O_6$ with a peak $(M + NH_4)^+$ at 314.



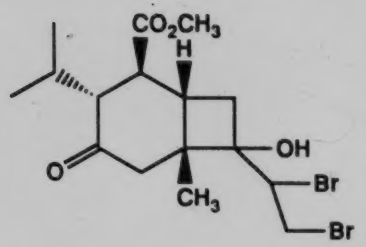
86



87

Another reaction which was pursued was formation of the α,β-unsaturated aldehyde, **87** by rearrangement of vinyl alcohol **62** using PDC. Hopefully, this compound could be easily epoxidized to form the spiro compound. Unfortunately, even after stirring with PDC for two days, no reaction had taken place. Again, forming the sp^2 center on the cyclobutane ring probably required too much energy to occur easily, and harsher conditions would likely lead to decomposition of the cyclobutane ring.

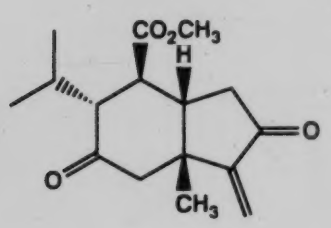
Another possible method of forming the spiro epoxide was to brominate the vinyl alcohol and then produce the epoxide from the resulting bromohydrin. Thus, we reacted vinyl alcohol **65** with bromine in carbon tetrachloride at 0°C. As this formed a mixture of compounds the reaction was repeated at a lower temperature and at -15°C two inseparable products were formed, dibromide **88** and a 5-10% yield of the ring expanded product! The dibromide showed a broad O-H band in the infrared spectrum centered around 3490 cm^{-1} and a strong carbonyl peak at 1712 cm^{-1} for the ketone. The ^1H NMR spectrum showed a peak at δ 4.40 as a doublet of doublets (J = 6, 7 Hz) for the proton adjacent to the secondary bromide. One of the protons adjacent to the primary bromide could be detected at δ 3.94 as a doublet of doublets (J = 6, 11 Hz), and the other was hidden in a multiplet at δ 3.60. Electron impact mass spectroscopy did not give the molecular ion peak, however chemical ionization gave three peaks corresponding to the various isotopes of the bromines for the formula $C_{16}H_{24}O_4Br_2$, $(M+NH_4)^+$: ^{81}Br-^{81}Br, 460; ^{81}Br-^{79}Br, 458; ^{79}Br-^{79}Br, 456.



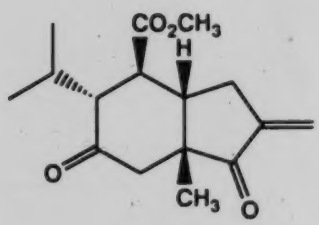
88

Ring expansions have been carried out on 1-vinylcycloalkanols using *tert*-butylhypochlorite.[49,50] This suggested that the possibility of using bromine as a source of bromonium ion for promoting the ring expansion was viable. In an attempt to improve upon the yield of the ring expansion product, vinyl alcohol **62** was reacted at -40°C with a freshly prepared 1% solution of bromine in dichloromethane. Two products could be isolated from the reaction, both being ring expansion products, with only a trace of dibromide being formed. The major ring expansion product was formed in 60% yield and contained approximately 5% of a dibromide impurity, while the minor was formed in 20% yield. The major product showed the following spectral data. Infrared spectroscopy showed two carbonyl stretches, one at 1716 cm^{-1} for the 6-membered ring ketone and one at 1732 cm^{-1} for the 5-membered ring ketone and the ester. Two distinctive peaks were visible in the ^1H NMR spectrum at δ 6.13 (s, 1H) and 5.32 (s, 1H) for the two protons on the exocyclic double bond. As these protons were seen as singlets, the regiochemistry of the ring expansion was assigned as in compound **89**. The methylene protons on the 5-membered ring showed at δ 2.70 and 2.23, each as a doublet of doublets with a geminal coupling constant of 19 Hz, suggesting they were adjacent to an

sp^2 center. HRMS showed a strong peak at 278.1516 for the formula $C_{16}H_{22}O_4$.



89

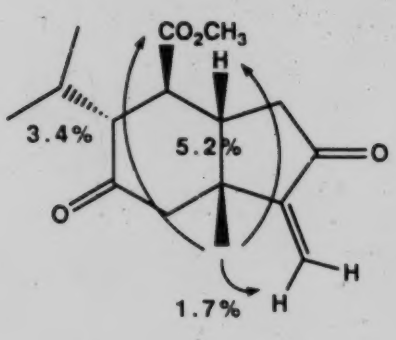


90

The second isomer gave a similar infrared spectrum with bands at 1736 and 1715 cm^{-1}. The two peaks for the exocyclic double bond (δ 6.20 and 5.52) were no longer singlets, but multiplets containing very small coupling constants. For this reason it was assigned the structure **90**. The methylene protons on the five membered ring (δ 2.92 and 2.40) showed a geminal coupling constant of 17 Hz. Again, mass spectroscopy confirmed the formula $C_{16}H_{22}O_4$ with a peak at 278.1516.

To further confirm the regiochemistry of the major isomer, NOE experiments were carried out. Unfortunately, the minor isomer was very unstable and comparative studies could not be undertaken. The results of the NOE study are shown below.

NOE Studies on Compound 89



The 1.7% enhancement seen between the irradiated methyl group and the olefinic proton confirmed that the regiochemistry of the ring expansion was in the desired direction. It also reconfirmed the *cis* relationship between the methyl ester, the methyl group and the ring junction hydrogen.

The ring expanded compound **89** contains all the carbons required for the dendrobine framework. What is left to accomplish is the addition of nitrogen to the α,β-unsaturated ketone, formation of the pyrollidine ring and lactonization. The pyrollidine ring could possibly be formed *via* a Hofmann-Loeffler-Freytag reaction of a haloamine,[51] while the lactonization has been accomplished by several other groups. Therefore, the crucial step remaining is the addition of a nitrogen unit to the ring system. At this point in the studies neither methylamine nor dimethylamine have been successfully added, with methylamine causing only decomposition of the starting material. Work is still in progress at this stage of the synthesis.

EXPERIMENTAL

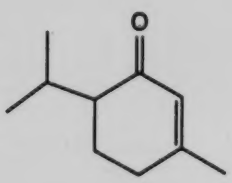
General

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Infrared spectra (FTIR) were determined using the following spectrophotometers: Nicolet 7199 FTIR and Nicolet MX-1 FTIR. Unless otherwise specified, all FTIR spectra were run in $CHCl_3$. High resolution mass spectra (HRMS) were obtained using a Kratos AE1 MS50 high resolution mass spectrometer and chemical ionization spectra (CIMS) on a Kratos AE1 MS12 spectrometer. Elemental analyses were determined by the microanalytical laboratory of this department. Proton nuclear magnetic resonance spectra (^1H NMR) were obtained using the following spectrometers: Bruker WH-200 (200 MHz), Bruker WH-400 (400 MHz) and Bruker AM-400 (400 MHz). Coupling constants are reported to within ±0.5 Hz and are weighted as in a first order spectra. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AM-400 (100.6 MHz) spectrometer. Unless otherwise specified, all NMR spectra were run in $CDCl_3$. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer-subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Values are quoted as percent enhancements and scaling values are not used when methyl groups are the irradiated signal. Optical rotations were determined in a Perkin-Elmer 241 polarimeter.

Materials

Flash chromatography was performed according to the procedure of Still[52] using silica gel of 230-400 mesh. All solvents were distilled previous to chromatography. Thin layer chromatography was performed on Merck aluminum-backed plates precoated with silica gel 60 GF_{254}. Solvents were purified as follows: diethyl ether, tetrahydrofuran (THF) and 1, 2-dimethoxyethane (DME) by distillation from a blue or purple solution of sodium benzophenone ketyl under an argon atmosphere; dimethyl sulfoxide (DMSO), dichloromethane, triethylamine (TEA), diisopropylamine and pyridine by distillation over calcium hydride; acetone by distillation over potasssium permanganate and benzene by distillation over lithium aluminium hydride.

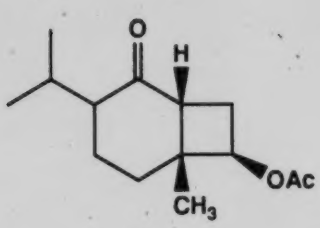
Piperitone (32).



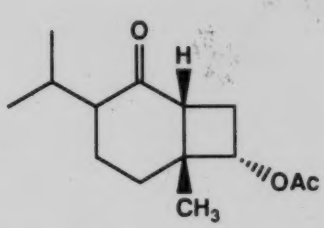
Piperitol (30 g, 0.2 mol) was dissolved in 400 mL of acetone in a 2L 3-necked flask equipped with a mechanical stirrer, condenser and addition funnel. Jones reagent (8N, 50 mL) was slowly added to the ice cooled mixture until the orange colour of the reagent persisted. The reaction was allowed to stir for 2 hours. The acetone was decanted and the chromate salts were washed with water (100 mL) and ether (3 X 50 mL). The liquids

were combined and the aqueous layer was removed. After drying over magnesium sulfate, the organic solution was concentrated and then purified by bulb-to-bulb distillation (79°C at 0.7 mm Hg) to generate 21.5 g (71% yield) of piperitone[53] (**32**) as a sweet smelling oil. $[\alpha]_D^{22}$ -20° ($CHCl_3$). ^1H NMR (200 MHz): δ 5.84 (s, 1H, -C**H**=), 2.30 (m, 3H), 1.90 (s, 3H, =CC**H**$_3$, overlapping m, 3H), 0.82 (d, J = 7 Hz, 3H, -CHC**H**$_3$), 0.92 (d, J = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 1669 (C=O) cm^{-1}. HRMS M^+: 152.1204 (calcd. for $C_{10}H_{16}O$ 152.1201). Anal. Calcd. for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.63; H, 10.52.

(*1R*, 6R*, 7R) and (*1R*, 6R*, 7S**)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-ones (38).**



Isomers I and II



Isomers III and IV

Piperitone (19.9 g, 0.13 mol) was dissolved in 800 mL of benzene and placed into the photocycloaddition reaction vessel along with vinyl acetate (15 eq, 180 mL). A steady stream of argon was continuously passed through the system and the entire apparatus was immersed in a large Dewar flask and kept ice cold throughout the reaction. The system was equipped with a 450 Watt mercury vapor lamp, pyrex filter, cooling jacket and condenser. After a 24 hour irradiation period, the solution was

concentrated and then redissolved in benzene (400 mL) and reacted with 1 equivalent (19.4 mL) of DBU at reflux for 24 hours.

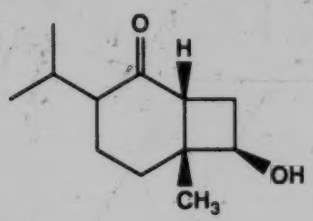
After concentration and rough purification through silica gel in a sintered glass funnel, 16.18 g (52%) of a mixture of the four isomers was isolated and used to determine the ratio of isomers by ^{1}H NMR analysis (4.5:2.8:2.2:1 for isomers 1:2:3:4). Further purification could be carried out by column chromatography on silica gel (gravity, 10 % ether / petroleum ether) to generate as a pure oil, isomer I. ^{1}H NMR (400 MHz): δ 4.90 (m, 1H, -C**H**OAc), 2.55 (m, 1H), 2.30 (m, 3H), 2.04 (s, 3H, -OCOC**H**$_3$), 1.98 (m, 3H), 1.66 (m, 1H), 1.46 (m, 1H), 1.22 (s, 3H, -CC**H**$_3$), 0.94 (d, J = 7 Hz, 3H, -CHC**H**$_3$), 0.86 (d, J = 7 Hz, 3H, -CHC**H**$_3$). ^{13}C NMR (100 MHz): δ 214 (C=O), 170.5 (acetate C=O), 69.41 (C-O), 55.8, 47.9, 45.8, 33.8, 29.0, 25.8, 23.4, 22.3, 20.81, 20.57, 18.43. FTIR (CH_2Cl_2 cast): 1739 (acetate C=O), 1705 (ketone C=O), 1239 (C-O) cm^{-1}. CIMS $(M+NH_4)^+$: 256.

Isomer II was obtained as an oil. ^{1}H NMR (400 MHz): δ 4.78 (t, J = 8 Hz, 1H, -C**H**OAc), 2.67 (ddd, J = 2.5, 8, 11.5 Hz, 1H, -C**H**CH$_2$CHOAc), 2.36 (ddd, J = 2.5, 1, 11 Hz, 1H, -C**H**HCHOAc), 2.28 (ddd, J = 11, 11.5, 8 Hz, -CH**H**CHOAc), 2.08 (s, 3H, -OCOC**H**$_3$, overlapping m, 1H), 1.90 (m, 3H), 1.64 (m, 2H), 1.24 (s, 3H, -CC**H**$_3$), 0.95 (d, J = 7 Hz, 3H, -CHC**H**$_3$), 0.84 (d, J = 7 Hz, 3H, -CHC**H**$_3$). FTIR (CH_2Cl_2 cast): 1741 (acetate C=O), 1705 (ketone C=O), 1300 (C-O) cm^{-1}. CIMS $(M+NH_4)^+$: 256.

Isomers III and IV were eluted as a 3:1 mixture of isomers showing the following spectral data. FTIR (CH_2Cl_2 cast): 1740 (acetate C=O), 1699 (ketone C=O), 1242 (C-O) cm^{-1}. CIMS $(M+NH_4)^+$: 256. The major isomer

showed the following ^{1}H NMR (200 MHz) data: δ 4.68 (m, 1H, -C**H**OAc), 2.7-2.1 (m),2.06 (s, 3H, -OCOC**H**$_3$), 1.5-1.4 (m), 1.25 (s, 3H, -CC**H**$_3$), 0.95 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.80 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). The minor isomer showed the following peaks in the ^{1}H NMR spectrum: δ 4.80 (t, 1H, -C**H**OAc), 2.08 (s, 3H, -OCOC**H**$_3$), 1.29 (s, 3H, -CC**H**$_3$), 0.95 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.85 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$).

(*1R*, 6R*, 7R)-7-Hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]-octan-2-ones (39).**

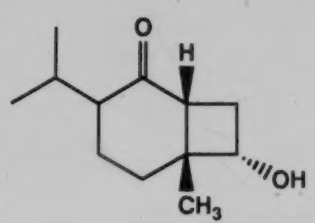


Isomer I of acetate **38** (65 mg, 0.27 mmol) was dissolved in 5 mL of 50% aqueous MeOH with 1.5 equivalents of Na_2CO_3 (45 mg) and was refluxed for 1 hour. After quenching with water (10 mL), the mixture was extracted into dichloromethane (3 X 20 mL), and the combined organic extracts were dried over sodium sulfate. Flash chromatography (50% ether / petroleum ether) produced two alcohols, the first isomer in 29% yield (15.7 mg) showing the following spectral data. ^{1}H NMR (400 MHz): δ 4.05 (t, *J* = 8 Hz, 1H, -C**H**OH), 2.58 (ddd, *J* = 2, 8, 10 Hz, 1H, -CH**H**CHOH), 2.22 (m, 1H), 2.12 (ddd, *J* = 8, 10, 11 Hz, 1H, -C**H**HCHOH), 1.96 (m, 2H), 1.78 (m, 1H), 1.50 (m, 1H), 1.25 (s, 3H, -CC**H**$_3$), 0.92 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.86 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR (CH_2Cl_2 cast): 3420 (O-H), 1699 (ketone C=O), 1109 (C-O) cm^{-1}. HRMS M$^+$: 196.1457 (calcd. for $C_{12}H_{20}O_2$ 196.1463).

A mixture of the two isomers (16.6 mg, 31%) eluted next, followed by the second alcohol (12.7 mg, 24%). ^{1}H NMR (400 MHz): δ 4.01 (dt, *J* = 1, 8 Hz, 1H, -C**H**OH), 2.68 (ddd, *J* = 3, 8, 12 Hz, 1H, -C**H**HCHOH), 2.30 (dt, *J* = 2, 10 Hz, 1H, -C**H**CH_2CHOH), 2.11 (ddd, *J* = 8, 10, 12 Hz, 1H, -CH**H**CHOH), 1.8 (m, 4H), 1.78 (m, 1H), 1.55 (ddd, *J* = 5, 10, 14.5, 1H, -CH_2C**H**$_2$C), 1.45 (ddd, *J* = 4.5, 6.5, 14.5, 1H, -CH_2C**H**$_2$C), 1.28 (s, 3H, -CC**H**$_3$), 0.94 (d, *J* = 6 Hz, 3H, -CHC**H**$_3$), 0.85 (d, *J* = 6 Hz, 3H, -CHC**H**$_3$). FTIR (CH_2Cl_2 cast): 3420 (O-H), 1701 (C=O), 1108 (C-O) cm^{-1}. HRMS M$^+$: 196.1457 (calcd. for $C_{12}H_{20}O_2$ 196.1463).

Isomer II of acetate **38** (50 mg, 0.21 mmol) was hydrolyzed using the same procedure as above. Two alcohols were produced in a total of 94% yield. The two alcohols were spectrally identical to the two alcohols produced from Isomer I.

(*1R*, 6R*, 7S)-7-Hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]-octan-2-ones (39).**

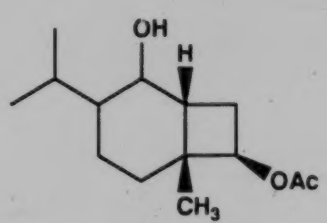


The mixture of Isomers III and IV from acetate **38** (39 mg, 0.16 mmol) were subjected to the same reaction conditions as described in the preceding experiment and two new alcohols were produced in quantitative yield. The first isomer (13.7 mg, 43%) showed the following spectra data. ^{1}H

NMR (400 MHz): δ 3.99 (m, 1H, -C**H**OH), 2.46 (ddd, *J* = 8, 9.5, 12 Hz, 1H, -C**H**HCHOH), 2.24 (m, 2H), 1.90 (m, 4H), 1.88 (bs, 1H, -O**H**), 1.25 (m, 2H), 1.21 (s, 3H, -CC**H**$_3$), 0.94 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.88 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR (CH_2Cl_2 cast): 3410 (O-H), 1692 (C=O) cm^{-1}. HRMS M$^+$: 196.1459 (calcd. for $C_{12}H_{20}O_2$ 196.1463).

The second alcohol (18.2 mg, 57%) gave similar spectral data. ^{1}H NMR (400 MHz): δ 3.86 (m, 1H, -C**H**OH), 2.53 (ddd, *J* = 7, 8, 10 Hz, 1H, -C**H**HCHOH), 2.28 (m, 2H), 2.15 (m, 2H), 2.02 (m, 3H), 1.54 (m, 2H), 1.18 (s, 3H, -CC**H**$_3$), 0.95 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.82 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3420 (O-H), 1695 (C=O), 1105 (C-O) cm^{-1}. HRMS M$^+$ 196.1461 (calcd. for $C_{12}H_{20}O_2$ 196.1463).

(*1R*, 6R*, 7R)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]-octan-2-ols (40).**



Isomer I of acetate **38** (4.2 g, 0.0175 mol) was dissolved in 30 mL of 95% ethanol. The solution was cooled to -10°C with a salt-ice bath and 2 molar equivalents of sodium borohydride (1.33 g) were slowly added. After 2 hours, the reaction was quenched with 1M HCl, and the mixture extracted into dichloromethane (3 X 50 mL). The combined organics were washed with saturated sodium chloride, dried over magnesium sulfate and concentrated. Flash chromatography (5% ethyl acetate / petroleum ether)

separated out two alcohols **40**. The first was a white solid (m.p. 90-91°C) and was formed in 76% yield (3.2 g) and showed the following spectral data. ^{1}H NMR (400 MHz): δ 4.95 (t, *J* = 8 Hz, 1H, -C**H**OAc), 4.06 (m, 1H, -C**H**OH), 2.36 (ddd, *J* = 2.5, 8, 11 Hz, 1H, -C**H**HCHOAc), 2.14 (ddd, *J* = 8, 10, 11 Hz, 1H, -CH**H**CHOAc), 2.04 (s, 3H, -OCOC**H**$_3$), 1.86 (m, 2H), 1.54 (m, 4H), 1.16 (ddd, *J* = 6, 10, 14 Hz, 1H, -CH$_2$C**H**HC), 1.08 (s, 3H, -CC**H**$_3$), 0.96 (d, *J* = 2.5 Hz, 3H, -CHC**H**$_3$), 0.94 (d, *J* = 2.5 Hz, 3H, -CHC**H**$_3$). FTIR: 3520 (O-H), 1737 (C=O), 1256 (C-O) cm^{-1}. CIMS (M + NH$_4$)$^+$: 258. Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.97, H, 10.06. Found: C, 69.97; H, 10.32.

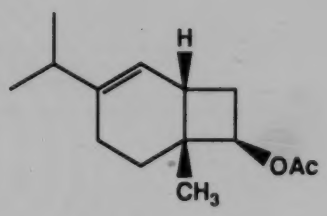
The second alcohol was isolated as an oil in 14% yield. ^{1}H NMR (400 MHz): δ 4.98 (t, *J* = 8 Hz, 1H, -C**H**OAc), 3.45 (m, 1H, -C**H**OH), 2.32 (dt, *J* = 11.5, 8 Hz, 1H, -C**H**HCHOAc), 2.15 (ddd, *J* = 2, 8, 11.5 Hz, 1H, -CH**H**CHOAc, overlapping m, 1H), 2.05 (s, 3H, -OCOC**H**$_3$), 1.77 (dt, *J* = 14, 3, 3 Hz, 1H, -CH$_2$C**H**HC), 1.53 (m, 4H), 1.14 (s, 3H, -CC**H**$_3$), 0.95 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.82 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3460 (O-H), 1738 (C=O), 1241 (C-O) cm^{-1}. CIMS (M + NH$_4$)$^+$: 258.

Isomer II of acetate **38** could be reduced under the same conditions. Therefore, 2.2 g (0.009 mol) of this compound was dissolved in 20 mL of 95% ethanol at -10°C and reacted with 0.7 g of sodium borohydride. After flash chromatography (5-25% ethyl acetate / petroleum ether), two alcohols were isolated in a total of 72% yield. The first isomer was isolated as a white solid (64-66°C) in 30% yield (0.64 g). ^{1}H NMR (400 MHz): δ 4.70 (dd, *J* = 3, 6.5 Hz, 1H, -C**H**OAc), 3.85 (d, *J* = 2.5 Hz, 1H, -C**H**OH), 2.35 (dt, *J* = 2.5, 9 Hz, 1H, -CHCH$_2$CHOAc), 2.15 (ddd, *J* = 13, 9, 6.5 Hz, 1H, -CH**H**CHOAc), 2.08 (s, 3H, -OCOCH$_3$), 1.94 (ddd, *J* = 3, 10, 13

Hz, 1H, -CHHCHOAc), 1.60 (m, 4H), 1.4 (m, 1H), 1.15 (m, 1H), 1.08 (s, 3H, $-CCH_3$), 0.95 (d, J = 1.5 Hz, 3H, $-CHCH_3$), 0.98 (d, J = 2.5 Hz, 3H, $-CHCH_3$). FTIR: 3500 (O-H), 1736 (C=O), 1244 (C-O) cm^{-1}. CIMS $(M + NH_4)^+$: 258.

The second alcohol was also isolated as a white solid (m.p. 63-64°C) in 42% yield (0.90 g). ^1H NMR (400 MHz): δ 4.74 (m, 1H, -CHOAc), 3.68 (m, 1H, -CHOH), 2.65 (ddd, J = 6, 9, 9 Hz, 1H, $-CHCH_2CHOAc$), 2.44 (ddd, J = 6, 9, 12.5 Hz, 1H, -CHHCHOAc), 2.15 (s, 3H, $-OCOCH_3$), 2.10 (m, 2H), 1.88 (ddd, J = 2, 9, 12.5 Hz, 1H, -CHHCHOAc), 1.60 (m, 3H), 1.44 (m, 1H), 1.05 (s, 3H, $-CCH_3$), 1.02 (d, J = 7 Hz, 3H, $-CHCH_3$), 0.86 (d, J = 7 Hz, 3H, $-CHCH_3$). FTIR: 3450 (O-H), 1739 (C=O), 1243 (C-O) cm^{-1}. CIMS $(M + NH_4)^+$: 258. Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.97; H, 10.06. Found: C, 69.76; H, 10.17.

(*1R*, 6R*, 7R)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]-oct-2-ene (36).**

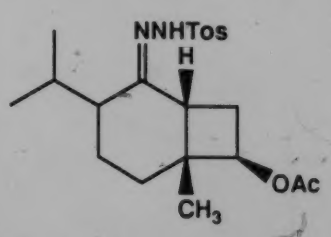


The major alcohol from isomer I of acetate **38** was eliminated in the following manner. The alcohol **40** (100 mg, 0.42 mmol) was dissolved in 5 mL of dichloromethane and cooled to 0°C. Thionyl chloride (2 eq, 0.06 mL) and pyridine (4 eq, 0.13 mL) were added and the mixture was allowed to warm to room temperature and then left stirring for 24 hours. The

mixture was quenched with saturated sodium bicarbonate solution and extracted into dichloromethane (3 X 20 mL), washed with 1M HCl (30 mL) to remove the pyridine and dried over magnesium sulfate. Flash chromatography (5% ether / petroleum ether) produced 86% (80 mg) of alkene **36** as a clear oil. ^{1}H NMR (400 MHz): δ 5.44 (bs, 1H, -C**H**=), 4.89 (t, *J* = 8 Hz, 1H, -C**H**OAc), 2.30 (ddd, *J* = 8, 10, 11Hz, 1H, -CH**H**CHOAc), 2.12 (m, 3H), 2.00 (s, 3H, -OCOC**H**$_3$, overlapping m, 1H), 1.90 (ddd, *J* = 3, 8, 11 Hz, 1H, -CH**H**CHOAc), 1.66 (ddd, *J* = 3, 5.5, 13.5 Hz, 1H, =CCH**H**), 1.12 (ddd, *J* = 11, 5.5, 13.5 Hz, 1H, =CC**H**H), 1.06 (s, 3H, -CC**H**$_3$), 0.96 (d, *J* = 6.5 Hz, 6H, -CH(C**H**$_3$)$_2$). FTIR: 1739 (C=O), 1236 (C-O) cm^{-1}. HRMS M$^+$: 222.1622 (calcd. for $C_{14}H_{22}O_2$ 222.1619). Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.64; H, 9.97. Found: C, 75.57; H, 9.78.

Under the same reaction conditions the second alcohol (84 mg) formed 27 mg (35%) of the same alkene. The alcohols formed from isomer II of acetate **38** were also reacted under the same conditions and formed alkene **36** in 22% and 25% yield, respectively.

(*1R*, 6R*, 7R)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]-octan-2-one *p*-toluenesulfonylhydrazones (41).**



The tosylhydrazone of isomer I of acetate **38** was produced by reacting 1.0 mmol (237 mg) of this compound with 2 equivalents (400 mg) of

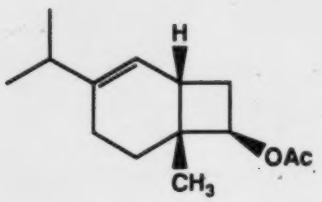
tosylhydrazine in 4 mL of methanol. The solution was refluxed for 7 hours, cooled, filtered and extracted into diethyl ether (3 X 30 mL). The organic layer was washed with saturated sodium chloride and dried over magnesium sulfate. Flash chromatography (50% ether / petroleum ether) generated two isomeric tosylhydrazones **41** in 69% yield (409 mg) in a ratio of 1:1.2. The first isomer (white solid, m.p. 150-152°C) showed the following spectral data. ^{1}H NMR (200 MHz): δ 7.85 (m, 2H, Ar), 7.25 (m, 2H, Ar), 4.26 (t, *J* = 7 Hz, 1H, -C**H**OAc), 2.65 (m), 2.40 (s, 3H, ArC**H**$_3$), 2.00 (s, 3H, -OCOC**H**$_3$), 1.70 (m), 1.60 (m), 1.25 (m), 1.10 (s, 3H, -CC**H**$_3$), 0.88 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.78 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3180 (N-H), 1739 (C=O), 1236 (C-O) cm^{-1}. HRMS M$^+$: 406.1943 (calcd. for $C_{21}H_{30}N_2O_4S$ 406.1926).

The second isomer was isolated as a solid with a m.p. of 134-139°C. ^{1}H NMR (400 MHz): δ 7.85 (m, 2H, Ar), 7.30 (m, 2H, Ar), 4.85 (t, *J* = 7 Hz, 1H, -C**H**OAc), 2.50 (m), 2.42 (s, 3H, ArC**H**$_3$), 2.03 (s, 3H, -OCOC**H**$_3$), 1.95 (m, 2H), 1.67 (m, 3H), 1.49 (m, 1H), 1.38 (m, 1H), 1.08 (s, 3H, -CC**H**$_3$), 0.74 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.29 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3181 (N-H), 1735 (C=O), 1238 (C-O) cm^{-1}. HRMS M$^+$: 406.1936 (calcd. for $C_{21}H_{30}N_2O_4S$ 406.1926).

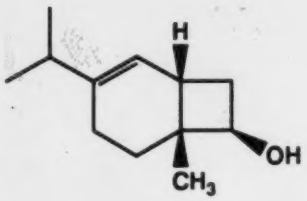
Isomer II of acetate **38** could be transformed into the same two tosylhydrazones (**41**) under the same reaction conditions in 58% yield with the recovery of 17% starting material.

(*1R*, 6R*, 7R)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]-oct-2-ene (36) and (*1R*, 6R*, 7R**)-7-Hydroxy-3-isopropyl-6-**

methylbicyclo[4.2.0]-oct-2-ene (42) *via* degradation of tosylhydrazones 41.



36



42

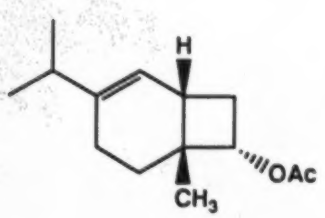
Sodium hydride (60% dispersion in oil, 2 eq, 19 mg) was washed twice with hexanes and then once with dry DMF. The first tosylhydrazone **41**, dissolved in 5 mL of DMF, was added to this and the resulting mixture brought to reflux. After 1.5 hours, the mixture was cooled and quenched with 10 mL of water. The mixture was extracted into hexanes (4 X 30 mL) to remove the DMF. The hexane layer was washed with brine, dried over magnesium sulfate and concentrated. Flash chromatography (5% ether / petroleum ether) produced 43 mg (80%) of pure alkene **36**.

The second tosylhydrazone (52 mg, 0.13 mmol) was eliminated under the same conditions, however it required a slightly longer reaction time (4 hours) which caused some cleavage of the acetate to occur. The reaction was worked up as described in the preceding experiment. Flash chromatography (5% ether / petroleum ether) produced 41% (12 mg) of alkene **36** and 35% (8 mg) of the deacetylated compound **42**. Alcohol **42** showed the following spectral data. ^{1}H NMR (400 MHz): δ 5.34 (bs, 1H, -C**H**=), 4.10 (m, 1H, -C**H**OH), 2.10 (m, 6H), 1.64 (ddd, J = 3, 5.5, 13.5 Hz, 1H, =CCH$_2$CH**H**), 1.50 (m, 1H), 1.22 (ddd, J = 6, 10, 13.5 Hz, 1H, =CCH$_2$C**H**H), 1.12 (s, 3H, -CC**H**$_3$), 1.00 (d, J = 7 Hz, 6H, -CH(C**H**$_3$)$_2$).

FTIR: 3320 (O-H), 1098 (C-O) cm^{-1}. HRMS M^+: 180.1505 (calcd. for $C_{12}H_{20}O$ 180.1514).

Alcohol **42** could be reacetylated to compound **36** in the following manner. Alcohol **42** (2.16 g, 0.012 mol) was mixed with 10 mL of pyridine and 2 mL of acetic anhydride and the solution was stirred at room temperature for 3 hours. The reaction was quenched with 1M HCl (100 mL), and then extracted into hexanes (3 X 75 mL). The combined organic extracts were washed with saturated sodium chloride solution and dried over magnesium sulfate. Bulb to bulb distillation at 62°C at 0.5 mm Hg produced 1.55 g (58% yield) of alkene **36**.

(*1R*, 6R*, 7S)-7-Acetoxy-3-isopropyl-6-methylbicyclo-[4.2.0]oct-2-ene (43).**

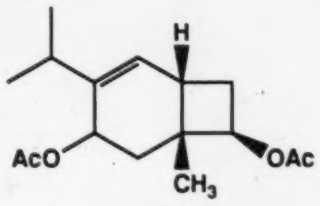


Isomers III and IV of acetate **38** (0.019 mol, 4.43 g) were dissolved in 50 mL of methanol along with 2 equivalents (7 g) of tosylhydrazine and 3 g of magnesium sulfate. After refluxing for 3.5 hours, the mixture was worked up as described previously for compound **41**. The crude reaction mixture was dissolved in 50 mL of DMF and added to pre-washed sodium hydride (1.5 g). The mixture was refluxed for 1.5 hours, cooled and worked up as described in the preceding experiment. After flash chromatography (5%-25% ether / petroleum ether) two compounds were isolated with the

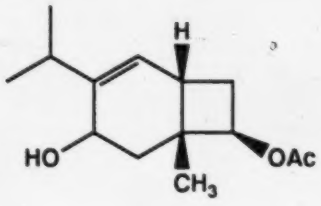
desired alkene **43** being the first compound eluted from the column in 20% yield (0.85 g). The alkene **43** showed the following spectral data. ^{1}H NMR (400 MHz): δ 5.38 (bs, 1H, -C**H**=), 4.66 (t, *J* = 8 Hz, 1H, -C**H**OAc), 2.46 (dt, *J* = 11, 8 Hz, 1H, -CH**H**CHOAc), 2.18 (septet, *J* = 7 Hz, 1H, -C**H**$(CH_3)_2$), 2.00 (s, 3H, -OCOC**H**$_3$), 1.90 (m, 1H), 1.90 (m), 1.66 (ddd, *J* = 5, 12, 12 Hz, 1H), 1.36 (dt, *J* = 13, 3.5 Hz, 1H), 1.14 (s, 3H, -CC**H**$_3$), 0.98 (d, *J* = 6.5 Hz, 6H, -CH(C**H**$_3$)$_2$). FTIR: 1743 (C=O), 1238 (C-O) cm^{-1}. HRMS M$^+$: 222.1621 (calcd. for $C_{14}H_{22}O_2$ 222.1619).

The deacetylated product was isolated in 34% yield (1.15 g) and showed the following spectral data. ^{1}H NMR (200 MHz): δ 5.3 (bs, 1H, -C**H**=), 3.82 (bt, 1H, -C**H**OAc), 2.40 (m), 1.06 (s, 3H, -CC**H**$_3$), 0.98 (d, 6H, -CH(C**H**$_3$)$_2$). FTIR: 3340 (O-H) cm^{-1}. HRMS M$^+$: 180.1514 (calcd. for $C_{12}H_{20}O$ 180.1514).

(*1R*, 6R*, 7R)-4,7-Diacetoxy-3-isopropyl-6-methyl-bicyclo[4.2.0]oct-2-ene (45) and (*1R*, 6R*, 7R**)-7-Acetoxy-4-hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-2-ene (46).**



45

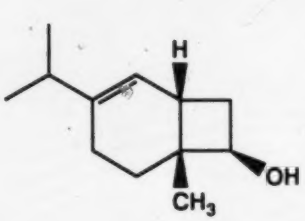


46

Alkene **36** (35 mg, 0.16 mmol) was dissolved in 2 mL of glacial acetic acid, 1.2 equivalents of selenium dioxide (21 mg) were added and the mixture brought to a reflux with stirring for 1 hour. The mixture was then

cooled, diluted with water and extracted into dichloromethane (3 X 25 mL). The organic layer was washed with water and dried over magnesium sulfate. Flash chromatography (10% to 50% ether / petroleum ether) produced 10 mg (23%) of diacetate **45** as an oil. ^{1}H NMR (200 MHz): δ 5.72 (d, *J* = 4 Hz, 1H, =C**H**), 5.41 (m, 2H, -C**H**OAc), 2.30 (m, 3H), 2.18 (s, 3H, -OCOC**H**$_3$), 2.14 (s, 3H, -OCOC**H**$_3$), 1.44 (dd, *J* = 5, 15 Hz, 1H), 1.08 (s, 3H, -CC**H**$_3$), 1.00 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 1.04 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 1735 (C=O), 1241 (C-O) cm^{-1}. HRMS M$^+$: 280.1679 (calcd. for $C_{16}H_{24}O_4$ 280.1674). Also isolated was 18% (7 mg) of allylic alcohol **46**. ^{1}H NMR (400 MHz): δ 5.50 (m, 1H, =C**H**), 4.78 (t, *J* = 8 Hz, 1H, -C**H**OAc), 4.52 (m, 1H, -C**H**OH), 2.68 (septet, *J* = 7 Hz, 1H, -C**H**(CH$_3$)$_2$), 2.34 (m, 2H), 2.14 (dd, *J* = 5.5, 11.5, 1H, -C**H**HCHOAc), 2.05 (s, 3H, -OCOC**H**$_3$), 1.94 (m, 1H), 1.30 (dd, *J* = 8, 11.5 Hz, 1H, -CH**H**CHOAc), 1.14 (s, 3H, -CC**H**$_3$), 1.06 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 1.05 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3440 (O-H), 1738 (C=O), 1242 (C-O) cm^{-1}. HRMS M$^+$: 238.1566 (calcd. for $C_{14}H_{22}O_3$ 238.1569).

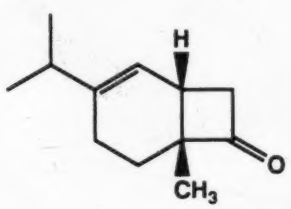
(*1R*, 6R*, 7R)-3-Isopropyl-6-methylbicyclo[4.2.0]oct-2-ene-7-ol (42).**



Alkene **36** (270 mg, 1.21 mmol) was dissolved in 50 mL of 50% aqueous methanol and mixed with 1.2 equivalents of potassium carbonate and refluxed for 3 hours. After cooling, the mixture was extracted into

dichloromethane (3 X 30 mL) and the combined organic extracts were washed with brine (30 mL) and dried over magnesium sulfate. Further purification was not required. The reaction yielded 210 mg (96% yield) of pure alcohol **42**. ^{1}H NMR (400 MHz): δ 5.34 (bs, 1H, -C**H**=), 4.10 (m, 1H, -C**H**OH), 2.10 (m, 6H), 1.64 (ddd, *J* = 3, 5.5, 13.5 Hz, 1H, =CCH$_2$CH**H**), 1.50 (m, 1H), 1.22 (ddd, *J* = 6, 10, 13.5 Hz, 1H, =CCH$_2$C**H**H), 1.12 (s, 3H, -CC**H**$_3$), 1.00 (d, *J* = 7 Hz, 6H, -CH(C**H**$_3$)$_2$). FTIR: 3320 (O-H), 1098 (C-O) cm^{-1}. HRMS M$^+$: 180.1505 (calcd. for $C_{12}H_{20}O$ 180.1514).

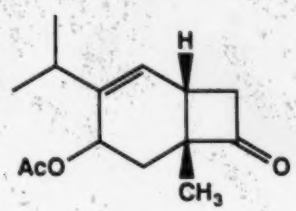
(*1R*, 6R)-3-Isopropyl-6-methylbicyclo[4.2.0]oct-2-en-7-one (49).**



Oxalyl chloride (1.1 eq, 0.11 mL) was dissolved in 5 mL of dry dichloromethane and cooled to -78°C. DMSO (2.2 eq, 0.18 mL) in 2 mL of CH_2Cl_2 was added from a dropping funnel, and then left for 2 minutes. The alcohol **42** (210 mg, 1.2 mmol) in 3 mL of CH_2Cl_2 was slowly added followed by 0.80 mL of triethylamine. The mixture was then slowly warmed to room temperature, at which time all starting material had disappeared. Quenching with water was followed by extraction into dichloromethane (3 X 30 mL), washing of the organic layers with saturated brine and drying over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) provided 178 mg (86%) of the desired cyclobutanone **49**. ^{1}H NMR (400 MHz): δ 5.58 (m, 1H, -C**H**=), 3.20 (dd, *J*

= 9, 17.5 Hz, 1H, -CHHC=O), 2.56 (dd, *J* = 5.5, 17.5 Hz, 1H, -CHHC=O), 2.42 (m, 1H, -CHCH$_2$C=O), 2.16 (septet, *J* = 7 Hz, 1H, -CHCH$_3$), 1.80 (m, 2H), 1.34 (m, 2H), 1.16 (s, 3H, -CCH$_3$), 0.94 (d, *J* = 7 Hz, 6H, -CH(CH$_3$)$_2$). FTIR: 1780 (C=O) cm^{-1}. HRMS M$^+$: 178.1359 (calcd. for $C_{12}H_{18}O$ 178.1358).

(*1R*, 6R)-4-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-2-en-7-one (50).**

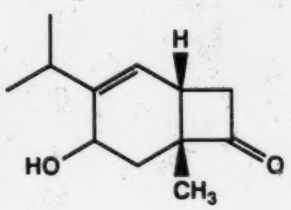


50

Enone **49** (100 mg, 0.57 mmol) was refluxed with 75 mg of selenium dioxide in 4 mL of glacial acetic acid and 2 mL of acetic anhydride. After 2 hours the mixture was cooled, diluted with water and extracted into dichloromethane (3 X 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (30 mL) and then dried over magnesium sulfate. Flash chromatography produced 63 mg (47%) of an inseparable mixture of two isomeric allylic acetates **50** (2:1 ratio). The mixture showed the following spectral data. FTIR: 1781 (cyclobutanone C=O), 1736 (acetate C=O), 1236 (C-O) cm^{-1}. HRMS M$^+$: 236.1410 (calcd. for $C_{14}H_{20}O_3$ 236.1412). The major isomer showed the following ^{1}H NMR data. ^{1}H NMR (200 MHz): δ 6.00 (d, *J* = 6 Hz, 1H, -CH=), 5.38 (t, *J* = 3 Hz, 1H, -CHOAc), 3.46 (dd, *J* = 8, 18 Hz, 1H, -CHHC=O), 2.80 (dd, *J* = 4, 18 Hz, 1H, -CHHC=O), 2.64 (m), 2.32 (m, 2H, overlapping dd, *J* = 3, 13 Hz,

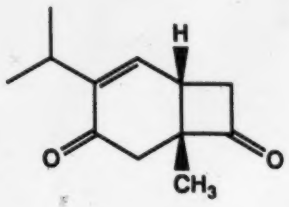
1H, -CH**H**CHOAc), 1.96 (s, 3H, -OCOC**H**$_3$), 1.42 (dd, *J* = 3, 14 Hz, 1H, -C**H**HCHOAc), 1.26 (s, 3H, -CC**H**$_3$), 1.04 (m, 6H, -CH(C**H**$_3$)$_2$). The minor isomer showed the following ^{1}H NMR data: δ 5.88 (m, 1H, =C**H**), 5.48 (m, 1H, -C**H**OAc), 2.08 (s, 3H, -OCOC**H**$_3$), 1.27 (s, 3H, -CC**H**$_3$), 1.04 (m, 6H, -CH(C**H**$_3$)$_2$).

(*1R*, 6R)-4-Hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-2-en-7-one (51).**



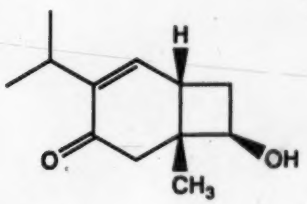
Potassium carbonate (1.2 equivalents, 250 mg) was dissolved in 10 mL of 75% aqueous methanol. Allylic acetates **50** (359 mg, 1.52 mmol) were added and the mixture refluxed for 1.5 hours. After cooling the mixture was extracted into dichloromethane (4 X 20 mL) and the combined organic layers were washed with water (30 mL) and dried over magnesium sulfate. Two compounds could be detected by TLC, however after column chromatography only one isomer could be isolated (191 mg, 65%), the other seemingly decomposed on the column. ^{1}H NMR (200 MHz): δ 5.65 (d, *J* = 4 Hz, 1H, -C**H**=), 4.32 (dd, *J* = 5, 6 Hz, 1H, -C**H**OH), 3.36 (m, 1H), 2.57 (m, 3H), 2.08 (dd, *J* = 5, 13.5 Hz, -CH**H**CHOH), 1.58 (dd, *J* = 7, 13.5 Hz, -C**H**HCHOH), 1.38 (s, 3H, -CHC**H**$_3$), 1.06 (t, *J* = 7 Hz, 6H, -CH(C**H**$_3$)$_2$). FTIR: 3450 (O-H), 1776 (C=O) cm^{-1}. HRMS M$^+$: 194.1299 (calcd. for $C_{12}H_{18}O_2$ 194.1307).

(*1R*, 6R)-4-Isopropyl-1-methylbicyclo[4.2.0]oct-4-ene-3,8-dione (44).**

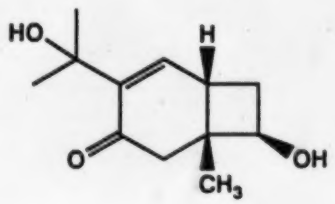


Allylic alcohol **51** (1 isomer, 129 mg, 0.66 mmol) was oxidized to the diketone through stirring overnight with PDC (1.5 eq, 348 mg), in 5 mL of dichloromethane at room temperature. The mixture was then filtered through Florasil to remove the chromate salts and then quickly passed through a short flash column using 30% ether / petroleum ether. Careful evaporation (due to volatility of the product) produced a quantitative yield of diketone **44** showing the following spectral data. ^{1}H NMR (400 MHz): δ 6.65 (d, *J* = 4 Hz, 1H, -C**H**=), 3.68 (dd, *J* = 7, 17 Hz, 1H, -C**H**HC=O), 2.94 (m, 2H), 2.80 (d, *J* = 18 Hz, 1H, -CC**H**HC=O), 2.75 (dd, *J* = 4, 17 Hz, 1H, -CH**H**C=O), 2.20 (d, *J* = 18 Hz, 1H, -CCH**H**C=O), 1.40 (s, 3H, -CHC**H**$_3$), 1.02 (m, 6H, -CH(C**H**$_3$)$_2$). FTIR: 1780 (cyclobutanone C=O), 1672 (enone C=O) cm^{-1}. HRMS M$^+$: 192.1128 (calcd. for $C_{12}H_{16}O_2$ 192.1150). Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.28.

(*1R*, 6R*, 8R)-8-Hydroxy-4-isopropyl-1-methylbicyclo[4.2.0]-oct-4-en-3-one (53) and (*1R*, 6R*, 8R**)-4-[(1-hydroxy-1-methyl)ethyl]-8-hydroxy-1-methylbicyclo[4.2.0]oct-4-en-3-one (54).**



53



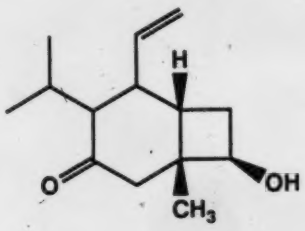
54

Alkene acetate **36** was transformed into compound **53** over three steps. Initial allylic oxidation was carried out by placing the alkene (2.60 g, 0.012 mol), selenium dioxide (1.2 eq, 1.6 g), pyridine (2 eq, 1.9 mL), ethanol (2 eq, 1.9 mL) and xylene (12 mL) into a preheated (140°C) oil bath. The mixture was stirred at reflux for 2 hours. After cooling, the reaction mixture was filtered over Celite and extracted into dichloromethane (3 X 50 mL). The organic layers were combined, washed with 1M HCl to remove the pyridine, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The mixture was partially concentrated, however the xylene was not evaporated as some of the volatile enone acetate **47** was formed during the reaction. The crude mixture was directly oxidized as column chromatography tended to decompose the allylic alcohols. Thus, the crude xylene solution was remixed with dichloromethane (50 mL) and reacted overnight at room temperature with 1.5 equivalents (6.1 g) of PDC. This produced the volatile enone acetate **47**, which was directly hydrolyzed by addition of 50 mL of 75% aqueous methanol and 2.4 g (1.5 eq) of potassium carbonate to the crude solution. After refluxing for 0.5 hour, the solution was cooled and extracted into dichloromethane

(3 X 50 mL). The organic layer was washed first with 1M HCl (50 mL) and then with saturated brine (50 mL) and dried over magnesium sulfate. The xylene could be removed by washing the crude material through a short layer of silica gel in a sintered glass funnel using ~200 mL of hexanes, followed by 100 mL of diethyl ether to elute the products. Flash chromatography (50% ether / petroleum ether) produced 960 mg (42%) of enone alcohol **53** as an oil, which distilled at 77°C at 0.15 mm Hg using a bulb to bulb distillation apparatus. ^{1}H NMR (400 MHz): δ 6.54 (d, *J* = 4 Hz, 1H, -C**H**=), 4.08 (m, 1H, -C**H**OH), 2.88 (septet, *J* = 7 Hz, 1H, -C**H**$(CH_3)_2$), 2.5 (m, 1H), 2.45 (d, *J* = 17 Hz, 1H, -CC**H**HC=O), 2.31 (ddd, *J* = 9, 11, 11 Hz, 1H, -C**H**HCHOH), 2.24 (d, *J* = 17 Hz, 1H, -CCH**H**C=O), 2.08 (ddd, *J* = 2.5, 8, 11 Hz, 1H, -CH**H**CHOH), 1.24 (s, 3H, -CC**H**$_3$), 1.03 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.98 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). ^{13}C NMR (100 MHz): δ 200.4 (C=O), 143.6 and 143.5 (C=C), 69.0 (C-O), 46.2, 42.4, 34.4, 33.4, 26.3, 21.8, 21.7, 19.9. FTIR: 3420 (O-H), 1669 (C=O) cm^{-1}. HRMS M$^+$: 194.1309 (calcd. for $C_{12}H_{18}O_2$ 194.1307). Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.99; H, 9.32.

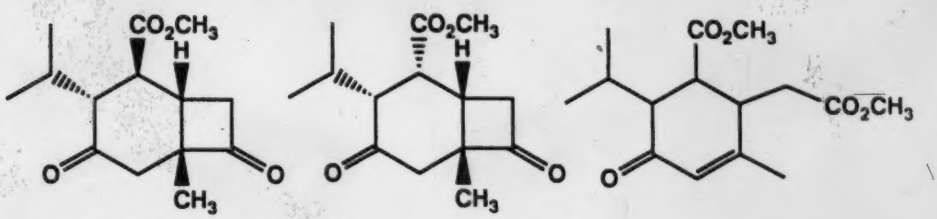
Also isolated in varying amounts (1-10%) was the overoxidized compound **54**. ^{1}H NMR (400 MHz): δ 6.80 (d, *J* = 4 Hz, 1H, -C**H**=), 4.08 (m, 1H, -C**H**OH), 2.55 (m, 1H), 2.46 (d, *J* = 17 Hz, 1H, -CC**H**HC=O), 2.34 (ddd, *J* = 8, 11, 12 Hz, 1H, -CH**H**CHOH), 2.32 (d, *J* = 17 Hz, 1H, -CCH**H**C=O), 2.12 (ddd, *J* = 3, 8, 11 Hz, 1H, -C**H**HCHOH), 1.41 (s, 3H, -C(OH)C**H**$_3$), 1.39 (s, 3H, -C(OH)C**H**$_3$), 1.24 (s, 3H, -CC**H**$_3$). FTIR: 3400 (O-H), 1655 (C=O) cm^{-1}. HRMS M$^+$: 210.1263 (calcd. for $C_{12}H_{18}O_3$ 210.1256).

(*1R*, 6R*, 8R)-8-Hydroxy-4-isopropyl-1-methyl-5-vinylbicyclo-[4.2.0]octan-3-ones (55).**



To a flame dried, argon cooled flask was added cuprous iodide (0.35 eq, 74 mg) and 3 mL of THF. This was cooled to 0°C and vinylmagnesium bromide (8 eq, 1M solution in THF, 0.9 mL) was slowly added. The mixture was stirred for 5 minutes and then cooled to -78°C. The enone alcohol **53** (243 mg, 1.1 mmol) in 5 mL of THF was slowly added and the mixture left for 0.5 hour and then quenched at this temperature with 1 M HCl. After warming to room temperature, the solution was extracted into dichloromethane (3 X 30 mL) and the organic layer washed with saturated sodium chloride (50 mL) and dried over magnesium sulfate. Flash chromatography produced 232 mg (83%) of an inseparable mixture of two isomers **55**. The ^{1}H NMR spectrum showed two sets of signals in a 2:1 ratio. The major isomer showed the following ^{1}H NMR (400 MHz) data: δ 5.34 (m, 1H, vinylic), 5.04 (m, 2H, vinylic), 4.25 (m, 1H, -C**H**OH), 2.58 (d, J = 13 Hz, 1H, -C**H**HC=O), 1.76 (dd, J = 3, 12 Hz, =CHC**H**), 1.45 (ddd, J = 3, 10, 12 Hz, -C**H**HCHOH), 1.08 (s, 3H, -CC**H**$_3$), 1.06 (d, J = 7 Hz, 3H, -CHC**H**$_3$), 0.89 (m, 3H, -CHC**H**$_3$). The minor isomer showed the following ^{1}H NMR (400 MHz) data: δ 5.68 (m, 1H, vinylic), 5.04 (m, 2H, vinylic), 4.10 (m, 1H, -C**H**OH), 1.20 (s, 3H, -CC**H**$_3$), 0.95 (m, 6H, -CHC**H**$_3$). The mixture also showed the following spectral data. FTIR: 3400 (O-H), 1704 (C=O) cm^{-1}. HRMS M$^+$: 222.1618 (calcd. for $C_{14}H_{22}O_2$ 222.1619).

(*1R*, 4R*, 5R*, 6R) and (*1R*, 4R*, 5S*, 6R**)-5-Carbomethoxy-4-isopropyl-1-methylbicyclo[4.2.0]octane-3,8-diones (56) and (57) and 4-[2-carbomethoxyethyl)]-5-carbomethoxy-4-isopropyl-1-methylcyclohex-2-en-1-one (58).**



56 **57** **58**

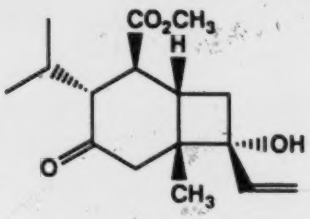
The mixture of vinylic compounds **55** could be oxidized to the diketo acids and then esterified using the following procedure. Ruthenium trichloride (12.2 mg, 2.2 mol %), sodium metaperiodate (4.1 eq, 1.86 g) and vinylic alcohols **55** (470 mg, 2.1 mmol) were mixed in a biphasic solution of 4 mL of CH_3CN, 4 mL of CCl_4 and 6 mL of H_2O. The mixture was stirred vigorously for 4 hours at room temperature. The layers were separated and the aqueous layer extracted into dichloromethane (6 X 20 mL). The combined organic layers were washed with brine (30 mL) and dried over magnesium sulfate. After concentration, the crude acid was esterified by mixing with 2 equivalents of potassium carbonate (0.59 g) and methyl iodide (3.3 eq, 0.44 mL) in dry acetone (10 mL) and stirring overnight. Flash chromatography (10% ether / petroleum ether) produced the two desired compounds in a combined 60% yield (328 mg) in a ratio of 75:25. The first isomer **56** showed the following spectral data. ^1H NMR (400 MHz): δ 3.75 (s, 3H, -COOC**H**$_3$), 3.48 (dd, J = 9, 18 Hz, 1H, -CHC**H**HC=O), 3.00 (dd, J = 4, 18 Hz, 1H, -CHCH**H**C=O), 2.92 (t, J = 12 Hz, 1H, -C**H**COOCH$_3$), 2.69 (d, J = 14 Hz, 1H, -CC**H**HC=O), 2.44 (dd, J = 4, 12 Hz,

1H, -CHCHCOOCH$_3$), 2.30 (ddd, J = 4, 9, 12 Hz, 1H, -CHCH$_2$C=O), 2.18 (d, J = 14 Hz, 1H, -CCHHC=O), 1.98 (dseptet, J = 3.5, 7 Hz, 1H, -CH(CH$_3$)$_2$), 1.28 (s, 3H, -CCH$_3$), 1.06 (d, J = 7 Hz, 3H, -CHCH$_3$), 0.88 (d, J = 7 Hz, 3H, -CHCH$_3$). ^{13}C NMR (100 MHz): δ 209.7 (C=O), 209.0 (C=O), 173.6 (C=O, ester), 60.7 (O-CH$_3$), 54.6, 52.2, 49.0, 47.8, 43.7, 34.6, 30.5, 21.9, 20.3, 18.2. FTIR: 1784 (cyclobutane C=O), 1736 (ester C=O), 1713 (cyclohexane C=O), 1170 (C-O) cm^{-1}. HRMS M$^+$: 252.1367 (calcd. for $C_{14}H_{20}O_4$ 252.1361).

The minor isomer **57** showed the following spectral properties. ^{1}H NMR (400 MHz): δ 3.74 (s, 3H, -COOCH$_3$, overlapping dd, J = 10, 18 Hz, 1H, -CHHC=O), 3.24 (dd, J = 3, 4 Hz, 1H, -CHCOOCH$_3$), 2.88 (dd, J = 4, 18 Hz, 1H, -CHHC=O), 2.78 (d, J = 19 Hz, 1H, -CCHHC=O), 2.69 (ddd, J = 3, 4, 10 Hz, 1H, -CHCH$_2$C=O), 2.48 (d, J = 19 Hz, 1H, -CCHHC=O), 2.27 (m, 1H, -CH(CH$_3$)$_2$), 2.18 (dd, J = 7, 3.5 Hz, 1H, -CHCH(CH$_3$)$_2$), 1.36 (s, 3H, -CCH$_3$), 1.01 (d, J = 7 Hz, 3H, -CHCH$_3$), 0.90 (d, J = 7 Hz, 3H, -CHCH$_3$). FTIR: 1781 (cyclobutane C=O), 1734 (ester C=O), 1715 (cyclohexane C=O) cm^{-1}. HRMS M$^+$: 252.1351 (calcd. for $C_{14}H_{20}O_4$ 252.1361).

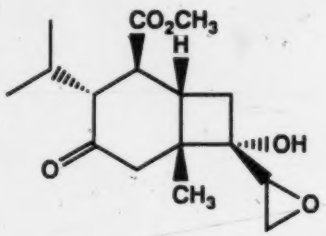
Also isolated from the reaction mixture in varying yields was the ring opened product **58**. ^{1}H NMR (400 MHz): δ 5.88 (s, 1H, -CH=), 3.73 (s, 3H, -COOCH$_3$), 3.72 (s, 3H, -COOCH$_3$), 3.17 (m, 1H, -CHCOOCH$_3$), 3.14 (m 1H), 2.66 (dd, J = 5, 17 Hz, 1H, -CHHCOOCH$_3$), 2.10 (m, 1H, -CH(CH$_3$)$_2$), 1.94 (s, 3H, -CCH$_3$), 1.06 (d, J = 7 Hz, 3H, -CHCH$_3$), 0.92 (d, J = 7 Hz, 3H, -CHCH$_3$). FTIR: 1738 (ester C=O), 1668 (enone C=O) cm^{-1}. HRMS M$^+$: 282.1460 (calcd. for $C_{15}H_{22}O_5$ 282.1467).

(*1R*, 4R*, 5R*, 6R*, 8R)-5-Carbomethoxy-8-hydroxy-4-isopropyl-1-methyl-8-vinylbicyclo[4.2.0]octan-3-one (62).**



Compound **56** (50.7 mg, 0.20 mmol) was dissolved in 5 mL of dry THF in a flame dried flask flushed with argon. The solution was cooled to -78°C and ~1.2 equivalents of vinyllithium (0.14 mL, 1.7M solution in THF) were slowly added. The reaction mixture was stirred for 1 hour at this temperature and was then quenched with 1M HCl. After warming to room temperature, the solution was extracted into dichloromethane (3 X 20 mL), the organic layer was then washed with brine (30 mL) and dried over magnesium sulfate. Flash chromatography (50% ether / petroleum ether) produced 41.3 mg (73%) of the vinyl addition product **62**. ^{1}H NMR (400 MHz): δ 6.02 (dd, *J* = 10, 17 Hz, 1H, -C**H**=CH$_2$), 5.45 (dd, *J* = 1, 17 Hz, 1H, -CH=C**H**H), 5.36 (dd, *J* = 10, 1 Hz, 1H, -CH=CH**H**), 3.73 (s, 3H, -COOC**H**$_3$), 2.89 (dd, *J* = 11.4, 11.5 Hz, 1H, -C**H**COOCH$_3$), 2.59 (d, *J* = 13 Hz, 1H, -C**H**HC=O), 2.44 (dd, *J* = 5, 13 Hz, 1H, -C**H**HCOH), 2.32 (m, 2H, -CH**H**COH, -C**H**CH(CH$_3$)$_2$), 2.10 (ddd, *J* = 11, 9, 5 Hz, 1H, -C**H**CH$_2$COH), 1.98 (d, *J* = 13 Hz, 1H, -CH**H**C=O), 1.96 (m, 1H, -C**H**(CH$_3$)$_2$), 1.16 (s, 3H, -CHC**H**$_3$), 1.01 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.85 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3450 (O-H), 1736 (ester C=O), 1712 (ketone C=O) cm^{-1}. CIMS (M+NH$_4$)$^+$: 298.

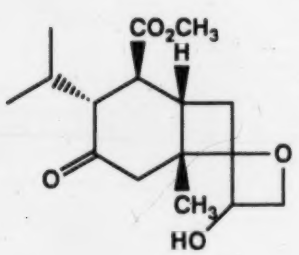
(*1R*, 2R*, 3R*, 6R*, 7R)-5-Carbomethoxy-8-(epoxyethyl)-8-hydroxy-4-isopropyl-1-methylbicyclo[4.2.0]octan-3-ones (63).**



Vinyl alcohol **62** (41 mg, 0.15 mmol) was dissolved in 2 mL of dichloromethane and cooled to 0°C. A solution of MCPBA (1.5 eq, 80% purity, 48 mg) in 2 mL of dichloromethane was slowly added and the mixture was allowed to stir for 24 hours at room temperature. The reaction was quenched with 5 mL of 10% sodium sulfite, and then washed with 10 mL of saturated sodium bicarbonate. The organic layer was washed with brine and dried over magnesium sulfate. Flash chromatography (50% ether / petroleum ether) separated two epoxides **63** in a total of 90% yield. The major epoxide (24 mg, 56%) showed the following spectral data. ^{1}H NMR (400 MHz): δ 3.74 (s, 3H, -COOC**H**$_3$), 3.38 (dd, *J* = 3, 4 Hz, 1H, -C**H**-O-CHH), 2.90 (t, *J* = 11 Hz, 1H, -C**H**COOCH$_3$, overlapping dd, *J* = 2.5, 5 Hz, -CH-O-CH**H**), 2.79 (d, *J* = 13.5 Hz, 1H, -C**H**HC=O, overlapping dd *J* = 4, 5 Hz, 1H, -CH-O-C**H**H), 2.38 (dd, *J* = 3, 11 Hz, 1H, -C**H**CH(CH$_3$)$_2$), 2.32 (dd, *J* = 9, 13.5 Hz, 1H, -CH**H**COH), 2.22 (d, *J* = 13.5 Hz, 1H, -CH**H**C=O), 2.18 (m, 1H), 2.09 (m, 1H), 2.04 (d septet, *J* = 3, 7 Hz, 1H, -C**H**CH$_3$)$_2$), 1.98 (d, *J* = 13 Hz, 1H, -CH**H**C=O), 1.14 (s, 3H, -CC**H**$_3$), 1.05 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.90 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3480 (O-H), 1734 (ester C=O), 1711 (ketone C=O) cm^{-1}. HRMS M$^+$: 296.1611 (calcd. for $C_{16}H_{24}O_5$ 296.1623).

The second isomer was isolated in 35% yield (15 mg). ^{1}H NMR (400 MHz): δ 3.70 (s, 3H, -COOC**H**$_3$), 3.15 (m, 1H, -C**H**COOCH$_3$), 3.04 (dd, *J* = 2.5, 4 Hz, 1H, -C**H**-O-CHH), 2.95 (d, *J* = 13 Hz, 1H, -C**H**HC=O), 2.84 (dd, *J* = 4, 5 Hz, 1H, -CH-O-C**H**H), 2.66 (dd, *J* = 2.5, 5 Hz, -CH-O-CH**H**), 2.32 (dd, *J* = 3, 12 Hz, 1H), 2.04 (m, 5H), 1.16 (s, 3H, -CC**H**$_3$), 1.04 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.90 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 3470 (O-H), 1734 (ester C=O), 1711 (ketone C=O) cm^{-1}. HRMS M$^+$: 296.1614 (calcd. for $C_{16}H_{24}O_5$ 296.1623).

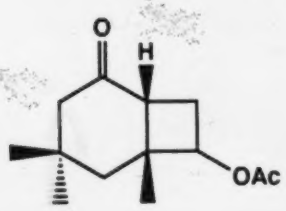
Spiro[(*1R*, 4R*, 5R*, 6R)-5-carbomethoxy-4-isopropyl-1-methylbicyclo[4.2.0]octan-3-one-8,2'-(3'-hydroxyl)-oxetane] (65).**



The major epoxide **63** was reacted with stannic chloride in the following manner. The epoxide (15.7 mg, 0.05 mmol) was dissolved in 2 mL of dry dichloromethane and cooled to 0°C. Stannic chloride (2 eq, 0.01 mL) was added and the mixture stirred at 0°C under argon for 0.5 hour. The reaction was quenched with saturated sodium bicarbonate solution and then extracted into dichloromethane (3 X 20 mL). The combined organic layers were washed with brine and then dried over magnesium sulfate producing 14 mg (89% yield) of the crude alcohol **65**. The crude product showed the following spectral data. ^{1}H NMR (400 MHz): δ 3.98 (dt, *J* = 9,

3 Hz, 1H, -CHOH), 3.74 (s, 3H, -COOCH$_3$), 3.64 (dd, J = 3, 11 Hz, 1H, -CHHCHOH, overlapping dd, J = 9, 11 Hz, 1H, -CHHCHOH), 2.65 (d, J = 13 Hz, 1H, -CHHC=O), 2.53 (m), 2.38 (dd, J = 3, 11 Hz, 1H), 2.05 (d septet, J = 3, 7 Hz, 1H, -CHCH$_3$)$_2$), 1.12 (s, 3H, -CCH$_3$), 1.04 (d, J = 7 Hz, 3H, -CHCH$_3$), 0.88 (d, J = 7 Hz, 3H, -CHCH$_3$). FTIR: 3470 (O-H), 1733 (ester C=O), 1713 (ketone C=O) cm^{-1}. HRMS M$^+$: 296.1637 (calcd. for $C_{16}H_{24}O_5$ 296.1623).

(*1R*, 6R)-7-Acetoxy-4,4,6-trimethylbicyclo[4.2.0]octan-2-ones (70).**

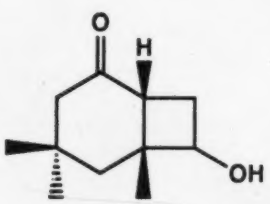


Isophorone (5 g, 0.036 mol) and vinyl acetate (50 mL, 15 eq) were dissolved into 200 mL of freshly distilled benzene and placed into the photoreaction vessel, following the procedure outlined previously for the photoaddition of piperitone and vinyl acetate. After 9 hours, the reaction was stopped and the solution concentrated, redissolved in benzene (100 mL) and refluxed with 1 equivalent (5.4 mL) of DBU overnight. The reaction mixture was cooled, concentrated and washed quickly through a short column of silical gel to remove the DBU. Flash chromatography (25% ether / petroleum ether) produced two isomeric acetates **70** in a total of 80% yield. The major isomer was formed in 61% yield (4.9 g). ^{1}H NMR (200 MHz): δ 4.92 (t, J = 7 Hz, 1H, -CHOAc), 2.44 (m, 3H), 2.20 (s, 2H, -CH$_2$C=O), 1.90 (d, J = 14 Hz, 1H, -CCHHC), 1.45 (d, J = 14 Hz, 1H,

-CCHHC), 1.21 (s, 3H, -CCH_3), 1.06 (s, 3H, -C(CH_3)$_2$), 0.98 (s, 3H, -C(CH_3)$_2$). FTIR: 1739 (acetate C=O), 1708 (ketone C=O) cm^{-1}. HRMS (M - $COCH_3$)+: 181.1225 (calcd. for $C_{11}H_{17}O_2$ 181.1228).

Isomer II of acetate **70**, isolated in 19% yield (1.5 g), showed the following spectral data. ^{1}H NMR (200 MHz): δ 4.65 (t, *J* = 8 Hz, 1H, -CHOAc), 2.10 (s, 3H, -OCOCH_3),1.36 (s, 3H, -CCH_3), 1.10 (s, 3H, -C(CH_3)$_2$), 0.92 (s, 3H, -C(CH_3)$_2$). FTIR: 1744 (acetate C=O), 1700 (ketone C=O) cm^{-1}. HRMS M+: 224.1408 (calcd. for $C_{13}H_{20}O_3$ 224.1412).

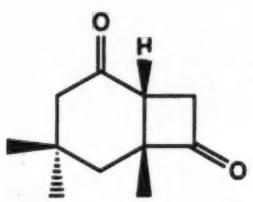
(*1R*, 6R)-7-Hydroxy-4,4,6-trimethylbicyclo[4.2.0]octan-2-one (71).**



Isomer I of acetate **70** (4.9 g, 0.02 mmol) was hydrolyzed to the alcohol by refluxing in 50 mL of 75% aqueous methanol with 1.4 equivalents (4.1 g) of potassium carbonate overnight. After cooling, the solution was extracted into dichloromethane (3 X 30 mL), the organic layer was washed with 30 mL of water, 30 mL of saturated sodium chloride solution and finally dried over magnesium sulfate. Flash chromatography (50% ether / petroleum ether) produced 2.85 g (72%) of the desired alcohol **71**. ^{1}H NMR (200 MHz): δ 4.10 (dd, *J* = 7, 14 Hz, 1H, -CHOH), 2.50 (m, 2H), 2.20 (s, 2H, -CH_2C=O), 2.13 (m, 2 H), 1.66 (d, *J* = 14 Hz, 1H, -CCHHC), 1.52 (d, *J* = 14 Hz, 1H, -CCHHC), 1.26 (s, 3H, -CCH_3), 1.04 (s, 3H, -C(CH_3)$_2$), 1.00

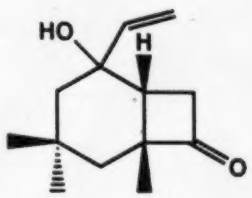
(s, 3H, -C(CH_3)$_2$). FTIR: 3420 (O-H), 1702 (C=O) cm^{-1}. HRMS M$^+$: 182.1310 (calcd. for $C_{11}H_{18}O_2$ 182.1307).

(*1R*, 6R)-4,4,6-Trimethylbicyclo[4.2.0]octane-2,7-dione (69).**



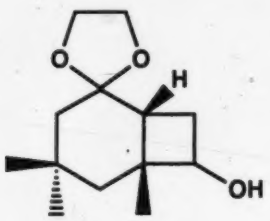
To a solution of 5 equivalents (2.7 mL) of DMSO in dichloromethane (70 mL) in a dry,argon flushed flask cooled to -10°C were added sequentially: 3 equivalents (3.4 mL) of phenyl dichlorophosphate, 5 equivalents (5.4 mL) of triethylamine and then 1 equivalent (1.4 g, 7.7 mmol) of alcohol **71** dissolved in 20 mL of dichloromethane. This mixture was stirred at -10°C for 5 minutes and then slowly warmed to room temperature. After 0.5 hour, 10 mL of water was added and the solution extracted into dichloromethane (3 X 30 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. Flash chromatography (50% ether / petroleum ether) gave 1.0 g (72%) of pure diketone **69** ^{1}H NMR (200 MHz): δ 3.52 (dd, *J* = 11, 18 Hz, 1H, -C**H**HC=O), 3.20 (dd, *J* = 5, 18 Hz, 1H, -CH**H**C=O), 2.68 (dd, *J* = 5, 11 Hz, 1H, -C**H**CH$_2$), 2.30 (d, *J* = 1Hz, 1H, -CC**H**HC=O), 2.28 (d, *J* = 1Hz, 1H, -CCH**H**C=O), 2.04 (d, *J* = 14 Hz, 1H, -CC**H**HC), 1.44 (d, *J* = 14 Hz, 1H, -CCH**H**C), 1.38 (s, 3H, -CC**H**$_3$), 1.04 (s, 3H, -C(C**H**$_3$)$_2$), 0.86 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1781 (cyclobutane C=O), 1709 (cyclohexane C=O) cm^{-1}. HRMS M$^+$: 180.1149 (calcd. for $C_{11}H_{16}O_2$ 180.1150).

(*1R*, 6R)-2-Hydroxy-4,4,6-trimethyl-2-vinylbicyclo[4.2.0]-octan-7-one (72).**



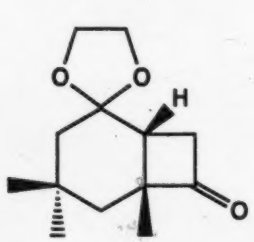
Vinyllithium (1.7M in THF, 0.2 eq, 1.96 mL) in 15 ml THF was cooled to -78°C. Diketone **69** (0.5 g, 2.8 mmol) was added and the mixture stirred under argon for 0.5 hour. The reaction was quenched with 10 mL of 1M HCl and extracted into dichloromethane (3 X 25 mL). The organic layers were washed with brine (30 mL) and dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) yielded 218 mg (38%) of the vinyl alcohol **72**. ^{1}H NMR (200 MHz): δ 6.04 (dd, *J* = 10, 17 Hz, 1H, -C**H**=CHH), 5.30 (d, *J* = 10 Hz, 1H, -CH=CH**H**), 5.14 (d, *J* = 17 Hz, 1H, -CH=C**H**H), 3.18 (dd, *J*= 18, 7 Hz, 1H, -C**H**HC=O), 3.06 (dd, *J*= 18, 9 Hz, 1H, -CH**H**C=O), 2.20 (dd, *J* = 7, 9 Hz, 1H, -C**H**CH_2C=O), 1.80 (d, *J* = 14 Hz, 1H, -C**H**H), 1.64 (d, *J* = 14 Hz, 1H, -CH**H**), 1.50 (d, *J* = 14 Hz, 1H, -C**H**H), 1.08 (d, *J* = 14 Hz, 1H, -CH**H**), 1.24 (s, 3H, -CC**H**$_3$), 1.00 (s, 6H, -C(C**H**$_3$)$_2$). FTIR: 3450 (O-H), 1771 (C=O) cm^{-1}. HRMS M$^+$: 208.1461 (calcd. for $C_{13}H_{20}O_2$ 208.1463).

(*1R*, 6R)-2,2-Ethylenedioxy-4,4,6-trimethylbicyclo[4.2.0]-octan-7-ol (73).**



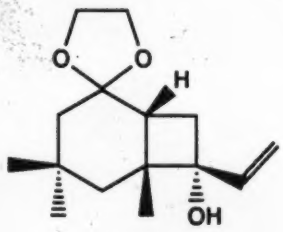
Keto-alcohol **71** (1.09 g, 0.006 mol) was placed in a Dean and Stark apparatus along with 50 mL of benzene, 5 mL of ethylene glycol and 0.3 equivalents (0.34 g) of *para*-toluenesulfonic acid. The mixture was refluxed for 8 hours, cooled and then washed with water (2 X 30 mL), saturated sodium chloride (30 mL) and then dried over magnesium sulfate. This produced 1.1 g (81%) of ketal **73** as an amorphous solid. ^{1}H NMR (200 MHz): δ 3.85 (m, 5H, -OC**H**$_2$ and -C**H**OH), 2.20 (m, 2H), 1.60 (d, *J* = 14 Hz, 1H, -C**H**H), 1.40 (d, *J* = 14 Hz, 1H, -CH**H**), 1.12 (s, 3H, -CC**H**$_3$), 1.04 (s, 3H, -C(C**H**$_3$)$_2$), 0.98 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 3395 (O-H) cm^{-1}. HRMS M$^+$: 226.1565 (calcd. for $C_{13}H_{22}O_3$ 226.1569). Anal. Calcd. for $C_{13}H_{22}O_3$: C, 72.49; H, 9.95. Found: C, 72.13; H, 9.75.

(*1R*, 6R)-2,2-Ethylenedioxy-4,4,6-trimethylbicyclo[4.2.0]-octan-7-one (74).**



To a dry, argon flushed flask cooled to -78°C was added 10 mL of dichloromethane. Oxalyl chloride (1.1 eq, 0.46 mL) and 2.2 equivalents (0.76 mL) of DMSO were added and stirred together for 5 minutes. Alcohol **73** (1.1 g, 4.9 mmol) was added, followed by 5 equivalents (3.4 mL) of triethylamine. The mixture was slowly warmed to room temperature and then quenched after 20 minutes with 10 mL of water. The layers were separated and the aqueous layer extracted with dichloromethane (2 X 30 mL). The combined organic layers were washed with 1M HCl to remove residual triethylamine, then washed with brine and dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) produced 0.93 g (85%) of ketone **74** as a clear oil. ^{1}H NMR (200 MHz): δ 4.0 (m, 4H, -OC**H**$_2$), 3.08 (d, *J* = 9 Hz, 2H, -C**H**$_2$C=O), 2.22 (dt, *J* = 1, 9 Hz, 1H, -C**H**CH$_2$C=O), 1.62 (d, *J* = 13.5 Hz, 1H, -CH**H**), 1.55 (m, 2H), 1.35 (d, *J* = 13.5 Hz, 1H, -CH**H**), 1.25 (s, 3H, -CC**H**$_3$), 1.06 (s, 3H, -C(C**H**$_3$)$_2$), 0.98 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1779 (C=O) cm^{-1}. HRMS M$^+$: 224.1408 (calcd. for $C_{13}H_{20}O_3$ 224.1412).

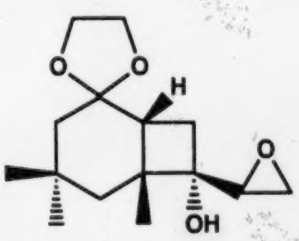
(*1R*, 6R*, 7R)-2,2-Ethylenedioxy-4,4,6-trimethyl-7-vinyl-bicyclo[4.2.0]octan-7-ol (75).**



THF (5 mL) in a dried argon flushed flask was cooled to -78°C along with 1.2 equivalents (0.44 mL of 1.7M solution in THF) of vinyllithium. To this was added ketone **74** (0.62 mmol, 139 mg) in 2 mL of THF. The mixture

was stirred under argon for 0.5 hour and then quenched with 1 M HCl. After warming to room temperature the mixture was extracted into dichloromethane (3 X 25 mL), the organic layers washed with brine and dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) produced compound **75** in 78% yield (121 mg). ^{1}H NMR (200 MHz): δ 6.08 (dd, *J* = 10, 17 Hz, -C**H**=CHH), 5.32 (dd, *J* = 1, 17 Hz, -CH=C**H**H), 5.18 (dd, *J* = 1, 10 Hz, -CH=CH**H**), 3.88 (m, 4H, -OC**H**$_2$), 1.72 (d, *J* = 14 Hz, 1H, -C**H**H), 1.44 (dt, *J* = 14, 2.Hz, 1H, -C**H**H), 1.08 (s, 6H, 2 X -C**H**$_3$), 1.02 (s, 3H, -C**H**$_3$). FTIR: 3580 (O-H) cm^{-1}. HRMS M+: 252.1722 (calcd. for $C_{15}H_{24}O_3$ 252.1725). Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.40; H, 9.58. Found: C, 71.02; H, 9.62.

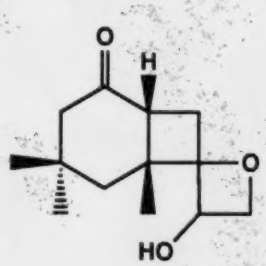
(*1R*, 6R)-7-(Epoxyethyl)-2,2-ethylenedioxy-4,4,6-trimethyl-bicyclo[4.3.0]octan-7-ols (77).**



The alkene **75** (139 mg, 0.55 mmol) was dissolved in 2 mL of dichloromethane and cooled to 0°C. MCPBA (1.5 eq, 179 mg, 80% purity) was dissolved in 2 mL of dichloromethane and added to the reaction vessel. The mixture was warmed to room temperature, stirred for 4 hours and then quenched with 10% sodium bisulfite. 10% Sodium bicarbonate solution was added and the mixture extracted into dichloromethane (3 X 30 mL). The organic layers were washed with brine and dried over magnesium sulfate. Flash chromatography produced an inseparable

mixture of epoxides **76** (2:1 ratio) in 83% yield (122 mg). The major isomer showed the following peaks in the ^{1}H NMR (200 MHz) spectrum: δ 3.95 (m, 4H, -OC**H**$_2$), 3.24 (dd, *J* = 3, 4 Hz, -C**H**-O-CHH), 2.80 (m, 2H, -C-H-O-C**H**$_2$), 1.22 (s, 3H, -CC**H**$_3$), 1.10 (s, 3H, -C(C**H**$_3$)$_2$), 1.00 (s, 3H, -C(C**H**$_3$)$_2$). The minor isomer showed the following distinctive peaks. δ 3.95 (m, 4H, -OC**H**$_2$), 3.40 (dd, *J* = 3, 4 Hz, -C**H**-O-CHH), 2.80 (m, 2H, -C-H-O-C**H**$_2$), 1.28 (s, 3H, -C**H**$_3$),1.10 (s, 3H, -C(C**H**$_3$)$_2$), 1.00 (s, 3H, -C(C**H**$_3$)$_2$). The mixture showed the following spectral data. FTIR: 3450 (O-H), 1093 (C-O) cm^{-1}. HRMS M$^+$: 268.1679 (calcd. for $C_{15}H_{24}O_4$ 268.1674).

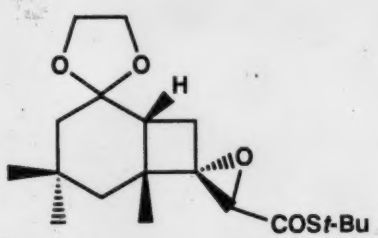
Spiro[(*1R*, 6R)-4,4,6-trimethylbicyclo[4.2.0]octan-2-one-7,2'-(3'-hydroxyl)-oxetane] (77).**



To a dry, argon flushed flask was added epoxy alcohols **76** (52 mg, 0.195 mmol) dissolved in 5 mL dichloromethane. The mixture was cooled to 0°C and 2 equivalents (0.045 mL) of stannic chloride was added. After 0.5 hour the mixture was quenched with saturated sodium bicarbonate solution and extracted into dichloromethane (3 X 20 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. Flash chromatography produced 5 mg (10%) of compound **77** along with 18 mg (42%) of the deketalized epoxides. ^{1}H NMR (400 MHz): δ 4.00 (dt,

J = 9, 3 Hz, 1H, -CHOH), 3.64 (dd, *J* = 3, 11 Hz, 1H, -OCHH), 3.58 (dd, *J* = 9, 11 Hz, 1H, -OCHH), 2.64 (s, 1H, -OH), 2.52 (d, *J* = 2 Hz, 1H), 2.41 (d, *J* = 17 Hz, 1H, -CHH), 2.32 (m, 2H), 2.18 (m, 3H), 1.48 (s, 3H, $-CCH_3$), 1.20 (d, *J* = 14 Hz, 1H), 1.08 (s, 3H, $-C(CH_3)_2$), 0.96 (s, 3H, $-C(CH_3)_2$). FTIR: 3210 (O-H), 1676 (C=O) cm^{-1}. HRMS M^+: 224.1391 (calcd. for $C_{13}H_{20}O_3$ 224.1412). ^{13}C-APT NMR (100 MHz): in phase 214.38 (C=O), 78.07 (C-O), 51.12, 47.35, 46.81, 40.39, 33.79, 32.50; antiphase 72.40 (CHOH), 45.40, 32.04, 32.04, 28.08, 26.03.

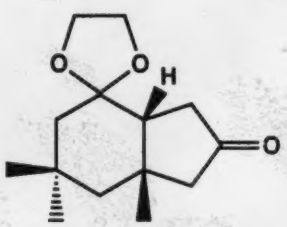
Spiro[(*1R*, 6R)-2,2-ethylenedioxy-4,4,6-trimethyl-bicyclo[4.2.0]octane-7,2'-(3'-*tert*-butylthiocarbonyl)-oxirane] (79).**



To a dried flask containing 3 mL of THF cooled to -78°C were added 2 equivalents (0.29 mL of 2.5 M solution in hexanes) of *n*-BuLi. Diisopropylamine (2.2 eq, 0.10 mL) dissolved in 3 mL of THF was added and the mixture was stirred under argon for 5 minutes. $BrCH_2COSC(CH_3)_3$ (2 eq, 155 mg) was slowly added to form the anion, followed by addition of ketone **74** (75 mg, 0.33 mmol). After 0.5 hour, the reaction was quenched with saturated ammonium chloride solution and the organic layer separated, washed with brine and dried over magnesium sulfate. Flash chromatography (10% ether / petroleum ether) produced 40.5 mg (34%) of the desired compound **79** and 29 mg (39%) of

recovered starting material. ^{1}H NMR (400 MHz): δ 4.00 (m, 2H, -OC**H**$_2$), 3.85 (m, 2H, -O-C**H**$_2$), 3.55 (s, 1H, -C-O-C**H**), 2.47 (dd, *J* = 10, 13 Hz, 1H, -CHC**H**H), 2.30 (dd, *J* = 9, 13 Hz, 1H, -CHCH**H**), 2.03 (t, *J* = 9, 10 Hz, 1H, -C**H**CHH), 1.85 (d, *J* = 14 Hz, 1H, -C**H**H), 1.67 (d, *J* = 14 Hz, 1H, -CH**H**), 1.49 (s, 9H, -C(C**H**$_3$)$_3$), 1.15 (s, 3H, -CC**H**$_3$), 1.05 (s, 3H, -C(C**H**$_3$)$_2$), 1.00 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1665 (C=O) cm^{-1}. HRMS M$^+$: 354.1861(calcd. for $C_{19}H_{30}O_4S$ 354.1865).

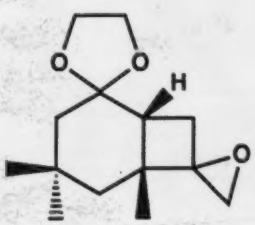
(*1R*, 6R)-2,2-Ethylenedioxy-4,4,6-trimethylbicyclo[4.3.0]-nonan-8-one (80).**



Epoxy thiol ester **79** (0.09 mmol, 33 mg) was dissolved in 1 mL of dioxane. Lithium iodide (1 eq, 12 mg) was added and the reaction mixture was brought to reflux and left for 8.5 hours. After cooling, saturated sodium chloride was added (10 mL), the layers separated and the organic layer dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) produced 9.5 mg (67%) of the ring expanded product **80**. ^{1}H NMR (400 MHz): δ 3.95 (m, 4H, -O-C**H**$_2$), 2.56 (d, *J* = 18 Hz, 1H, -C**H**H), 2.38 (dd, *J* = 8.5, 19 Hz, 1H, -CHC**H**H), 2.24 (dd, *J* = 5.5, 19 Hz, 1H, -CHCH**H**), 2.18 (dd, *J* = 8, 5.5 Hz, 1H, -C**H**CHH), 1.90 (d, *J* = 18 Hz, 1H, -CH**H**), 1.64 (d, *J* = 14 Hz, 1H, -C**H**H), 1.48 (d, *J* = 14.5 Hz, 1H, -C**H**H), 1.38 (d, *J* = 14 Hz, 1H, -CH**H**), 1.30 (d, *J* = 14.5 Hz, 1H, -CH**H**), 1.10 (s, 3H,

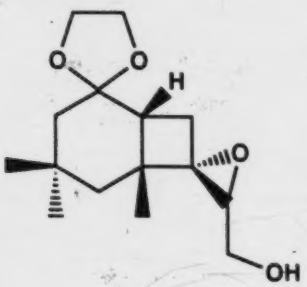
-CC**H**$_3$), 1.04 (s, 3H, -C(C**H**$_3$)$_2$), 1.02 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1742 (C=O) cm^{-1}. HRMS M$^+$: 238.1531 (calcd. for $C_{14}H_{22}O_3$ 238.1569).

Spiro[(*1R*, 6R)-2,2-ethylenedioxy-4,4,6-trimethylbicyclo[4.2.0]octane-7,2'-oxirane] (81).**



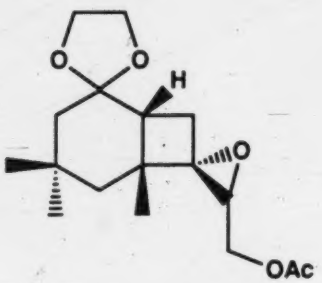
A suspension of sodium hydride (60% dispersion in oil, 2.25 eq, 35 mg) in 1 mL of DMSO was heated at 70°C for 1 hour and then cooled. THF (0.3 mL) was added and the solution was further cooled to 0°C. To this were added 2.6 equivalents (197 mg) of trimethylsulfonium iodide in 0.3 mL of DMSO followed 2-3 minutes later by ketone **74** (0.39 mmol, 87 mg) in a small amount of THF. After 30 minutes the ice bath was removed and the reaction allowed to warm to room temperature over 1.5 hours. The reaction mixture was then diluted with water and extracted into ether (3 X 20 mL) and the combined ether extracts dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) gave 59 mg (63%) of the epoxide **81**. ^{1}H NMR (400 MHz): δ 3.92 (m, 4H, -OC**H**$_2$), 2.88 (dd, *J* = 1, 5 Hz, 1H, -C-O-CH**H**), 2.68 (d, *J* = 5 Hz, 1H, -C-O-CH**H**), 2.40 (bt, *J* ~ 11 Hz, 1H, -CHC**H**H), 2.24 (dd, *J* = 9, 12 Hz, 1H, -C**H**CH$_2$), 2.04 (bt, *J* ~ 11 Hz, 1H, -CHCH**H**), 1.85 (d, *J* = 14 Hz, 1H, -C**H**H), 1.38 (m), 1.20 (dd, *J* = 14, 2 Hz, 1H, -C**H**H), 1.10 (s, 3H, -CC**H**$_3$), 1.06 (s, 3H, -C(C**H**$_3$)$_2$), 1.00 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1095 (C-O) cm^{-1}. HRMS M$^+$: 238.1569 (calcd. for $C_{14}H_{22}O_3$ 238.1569).

Spiro[(*1R*, 6R)-2,2-ethylenedioxy-4,4,6-trimethyl-bicyclo[4.2.0]octane-7,2'-(3'-hydroxymethyl)-oxirane] (78).**



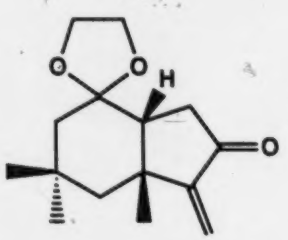
Epoxy thiol ester **79** (43 mg, 0.12 mmol) was dissolved in 95% ethanol (2 mL). Sodium borohydride (4 molar eq, 18.4 mg) was added and the mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched by slow addition of saturated ammonium chloride. The mixture was extracted into dichloromethane (3 X 20 mL) and the combined organic extracts were washed with water (20 mL), saturated sodium chloride (20 mL) and then dried over magnesium sulfate. Flash chromatography (3% methanol / chloroform) produced the alcohol **78** in 75% yield (24.4 mg). ^{1}H NMR (400 MHz): δ 3.90 (m, 4H, -O-C**H**$_2$), 3.58 (bdd, J = 6, 12 Hz, 1H, -C-O-C**H**), 3.20 (dd, J = 6, 3.5 Hz, 1H, -C**H**HOH), 2.35 (dd, J = 10, 12.5 Hz, 1H, -CHC**H**H), 2.20 (dd, J = 9, 12.5 Hz, 1H, -CHCH**H**), 1.95 (dd, J = 9, 10 Hz, 1H, -C**H**CH$_2$), 1.82 (d, J = 14.5 Hz, 1H, -C**H**H), 1.70 (bs, 1H, -O-**H**), 1.65 (d, J = 14 Hz, 1H, -C**H**H), 1.48 (d, J = 14.5 Hz, 1H, -CH**H**), 1.12 (s, 3H, -CC**H**$_3$), 1.05 (s, 3H, -C(C**H**$_3$)$_2$), 1.00 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 3430 (O-H), 1092 (C-O) cm^{-1}. HRMS M+: 268.1663 (calcd. for $C_{15}H_{24}O_4$ 268.1674).

Spiro[(*1R*, 6R)-2,2-ethylenedioxy-4,4,6-trimethyl-bicyclo[4.2.0]octane-7,2'-(3'-acetoxymethyl)-oxirane] (82).**



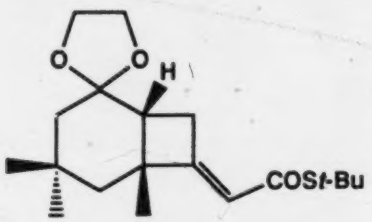
Epoxy alcohol **78** (12 mg, .044 mmol) was mixed with 1 mL of dry pyridine and 0.25 mL acetic anhydride. The mixture was stirred overnight and then extracted into dichloromethane (3 X 15 mL). The extracts were washed with 1M HCl (10 mL), brine (10 mL) and then dried over magnesium sulfate. Flash chromatography gave 7 mg (50%) of the desired acetate **82**. ^{1}H NMR (400 MHz): δ 4.32 (dd, *J* = 4, 12 Hz, 1H, -C**H**HOAc), 4.00 (m, 2H, --OC**H**$_2$), 3.85 (m, 3H, -OC**H**$_2$, -CH**H**OAc), 3.25 (dd, *J* = 4, 7 Hz, 1H, -C-O-C**H**), 2.38 (dd, *J* = 10, 13 Hz, 1H, -CHC**H**H), 2.24 (dd, *J* = 9, 13 Hz, 1H, -CHCH**H**), 2.10 (s, 3H, -OCOC**H**$_3$), 1.80 (d, *J* = 15 Hz, 1H, -C**H**H), 1.65 (d, *J* = 14 Hz, 1H, -CH**H**), 1.58 (t, *J* = 10 Hz, 1H, -C**H**CH$_2$), 1.50 (dt, *J* = 14, 1 Hz, 1H, -C**H**H), 1.18 (dd, *J* = 15, 1 Hz, 1H, -CH**H**), 1.12 (s, 3H, -CC**H**$_3$), 1.05 (s, 3H, -C(C**H**$_3$)$_2$), 1.02 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1745 (C=O), 1234 (C-O) cm^{-1}. HRMS (M-OAc)$^+$: 251.1645 (calcd. for $C_{15}H_{23}O_3$ 251.1647).

(*1R*, 6R)-2,2-Ethylenedioxy-7-methylene-4,4,6-trimethyl-bicyclo[4.3.0]non-8-one (83).**



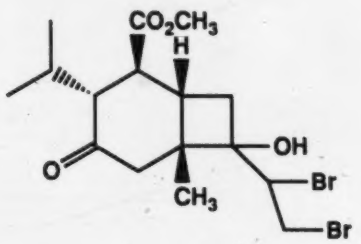
Epoxy acetate **82** (6 mg, 0.02 mmol) was dissolved in 1 mL of dioxane. Lithium iodide (1 eq, 3 mg) was added and the mixture was brought to reflux and left for 22 hours. After cooling, water was added and the mixture was extracted into dichloromethane (3 X 20 mL). The combined organic extracts were washed with saturated brine and dried over magnesium sulfate. Flash chromatography (25 % ether / petroleum ether) produced 3 mg (60%) of the desired ring expansion product **83**. ^{1}H NMR (400 MHz): δ 5.96 (s, 1H, -C=C**H**H), 5.16 (s, 1H, -C=CH**H**), 3.92 (m, 4H, -O-C**H**$_2$), 2.45 (dd, *J* = 7.5, 18 Hz, 1H, -CHC**H**H), 2.34 (dd, *J* = 4.5, 18 Hz, 1H, -CHCH**H**), 2.15 (dd, *J* = 4.5, 7.5 Hz, 1H, -C**H**CH$_2$), 1.80 (dd, *J* = 1, 14.5 Hz, 1H, -C**H**H), 1.62 (dd, *J* = 1.5, 13.5 Hz, 1H, -C**H**H), 1.40 (d, *J* = 14.5, Hz, 1H, -CH**H**), 1.35 (d, *J* = 13.5 Hz, 1H, -CH**H**), 1.24 (s, 3H, -CC**H**$_3$), 1.14 (s, 3H, -C(C**H**$_3$)$_2$), 0.94 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1728 (C=O), 1634 (C=C) cm^{-1}. HRMS M$^+$: 250.1568 (calcd. for $C_{15}H_{22}O_3$ 250.1569).

(*1R, *6R**)-2,2-Ethylenedioxy-7-*S*-*tert*-butylthiocarbonyl-methylene-4,4,6-trimethylbicyclo[4.2.0]octane (85).**



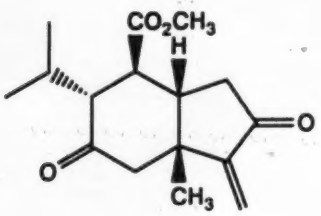
To a cooled (0°C) slurry of sodium hydride (60% dispersion in oil, 14 mg, 1 eq) in DME (0.5 mL) was slowly added $(EtO)_2POCH_2COSt$-Bu (1.2 eq, 96 mg). The mixture was stirred until all bubbling ceased, indicating complete formation of the anion. The reaction was warmed to room temperature and ketone **74** (76 mg, 0.34 mmol) was added. The mixture was left stirring under argon overnight and was then quenched with 1M HCl, followed by extraction into ether (3 X 30 mL). The combined organic extracts were washed with saturated sodium chloride and then dried over magnesium sulfate. Flash chromatography gave 45 mg (39%) of the α,β-unsaturated thiol ester **85**, along with 15 mg (20%) of recovered starting material. ^{1}H NMR (200 MHz): δ 5.85 (t, *J* = 2 Hz, 1H, -C=C**H**), 3.90 (m, 4H, -O-C**H**$_2$), 3.22 (ddd, *J* = 2, 9, 18 Hz, 1H, -CHC**H**H), 2.98 (ddd, *J* = 2, 8, 18 Hz, 1H, -CHCH**H**), 2.22 (ddd, *J* = 8, 9, 1.5 Hz, 1H, -C**H**CH$_2$), 1.68 (d, *J* = 14 Hz, 1H, -C**H**H), 1.58 (d, *J* = 14 Hz, 1H, -CH**H**), 1.50 (s, 9H, -C(C**H**$_3$)$_3$), 1.24 (s, 3H, -CC**H**$_3$), 1.04 (s, 3H, -C(C**H**$_3$)$_2$), 0.98 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 1675 (C=O), 1638 (C=C) cm^{-1}. HRMS M$^+$: 338.1926 (calcd. for $C_{19}H_{30}O_3S$ 338.1916).

(*1R*, 4R*, 5R*, 6R*, 8R)-5-Carbomethoxy-8-(1,2-dibromoethyl) -8-hydroxy-4-isopropyl-1-methylbicyclo[4.2.0]octan-3-one (88).**

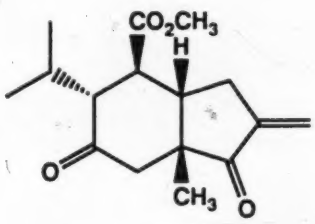


Vinyl alcohol **62** (30 mg, 0.11 mmol) was dissolved in 3 mL of carbon tetrachloride in a dry, argon flushed flask, and then cooled to -15°C. The solution was titrated with a 1% solution of bromine in carbon tetrachloride, until the bromine colour persisted. Saturated sodium hydrogen carbonate solution was added and the mixture stirred until all the bromine had disappeared. The mixture was extracted into dichloromethane (3 X 20 mL) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) gave 28 mg (58%) of the dibromide **88** contaminated with ~ 5% of the ring expanded product. ^{1}H NMR (200 MHz): δ 4.40 (dd, J = 6, 7 Hz, 1H, -C**H**Br), 3.94 (dd, J = 6, 11 Hz, 1H, -C**H**Br), 3.70 (s, 3H, -COOC**H**$_3$), 3.60 (m, 2H), 2.78 (dd, J = 8, 10.5 Hz, 1H, -CHC**H**H), 2.0-2.5 (m), 1.10 (s, 3H, -CHC**H**$_3$), 1.0 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)$_2$), 0.82 (d, J = 7 Hz, 3H, -CH(C**H**$_3$)$_2$). FTIR: 3490 (O-H), 1720 (broad, C=O) cm^{-1}. CIMS (M+ NH_4)$^+$: 460 (^{81}Br-^{81}Br), 458 (^{81}Br-^{79}Br), 456 (^{79}Br-^{79}Br).

(*1R*, 4R*, 5R*, 6R)-5-Carbomethoxy-4-isopropyl-1-methyl-9-methylenebicyclo[4.3.0]nonane-3,8-dione (90) and (*1R*, 4R*, 5R*, 6R**)-5-Carbomethoxy-4-isopropyl-1-methyl-8-methylenebicyclo[4.3.0]nonane-3,9-dione (89).**



90



89

To a dry, argon flushed flask was added vinyl alcohol **62** (29.5 mg, 0.105 mmol) in dichloromethane (7 mL). The solution was cooled to -40°C and a freshly prepared 1% solution (1 eq, 0.54 mL) of bromine in dichloromethane was added over 20 minutes. The mixture was quenched with saturated sodium bicarbonate solution and then extracted into dichloromethane (3 X 15 mL). The combined organic extracts were washed with brine (20 mL) and dried over magnesium sulfate. Flash chromatography (25% ether / petroleum ether) produced two compounds, both products of ring expansion. The minor compound **90** was isolated in 20% yield (6 mg) and showed the following spectral data. ^{1}H NMR (400 MHz): δ 6.20 (m, 1H, -C=C**H**H), 5.52 (m, 1H, -C=CH**H**), 3.74 (s, 3H, -COOC**H**$_3$), 2.92 (dddd, *J* = 3, 3, 11, 17 Hz, 1H, -CHC**H**H), 2.60 (d, *J* = 14 Hz, 1H, -CC**H**H), 2.40 (dm, *J* = 17 Hz, 1H, -CHCH**H**), 2.32 (d *J* = 14 Hz, 1H, -CCH**H**), 2.28 (ddd, *J* = 1, 8, 12 Hz, -C**H**CHH), 1.85 (d septet, *J* = 4, 7 Hz, 1H, -C**H**(CH$_3$)$_2$), 1.14 (s, 3H, -CC**H**$_3$), 0.98 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.88 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 1736 (ester C=O), 1715 (ketone C=O) cm^{-1}. HRMS M$^+$: 278.1516 (calcd. for $C_{16}H_{22}O_4$ 278.1518).

The second product was the desired ring expansion product **89** and was isolated in 60% yield (17.5 mg). ^{1}H NMR (400 MHz): δ 6.13 (s, 1H, -C=C**H**H), 5.32 (s, 1H, -C=CH**H**), 3.74 (s, 3H, -COOC**H**$_3$), 2.70 (dd, *J* = 8, 19 Hz, 1H, -CHC**H**H), 2.58 (m, 3H), 2.38 (m, 1H), 2.23 (dd, *J* = 1, 19 Hz, 1H, -CHCH**H**), 1.85 (m, 1H, -C**H**(CH$_3$)$_2$), 1.24 (s, 3H, -CC**H**$_3$), 0.99 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$), 0.88 (d, *J* = 7 Hz, 3H, -CHC**H**$_3$). FTIR: 1732 (ester C=O), 1716 (ketone C=O) cm^{-1}. HRMS M$^+$: 278.1516 (calcd. for $C_{16}H_{22}O_4$ 278.1518).

REFERENCES

1. Suzuki, H.; Keimatsu, I., *J. Pharm. Soc. Jpn.*, **52**, 1049 (1932).
2. Yamamura, S.; Hirata, Y., *Tetrahedron Lett.*, 79 (1964).
3. Inubushi, Y.; Sasaki, Y.; Tsuda, Y.; Yasui, B.; Konita, T.; Matsumoto, J.; Katarao, E.; Nakano, J., *Tetrahedron*, **20**, 2007 (1964).
4. Onaka, T.; Kamata, S.; Maeda, T.; Kawazoe, Y.; Natsume, M.; Okamoto, T.; Uchimaru, F.; Shimizu, M., *Chem. Pharm. Bull. (Tokyo)*, **12**, 506 (1964).
5. Onaka, T.; Kamata, S.; Maeda, T.; Kawazoe, Y.; Natsume, M.; Okamoto, T.; Uchimaru, F.; Shimizu, M., *Chem. Pharm. Bull. (Tokyo)*, **13**, 745 (1965).
6. Okamoto, T.; Natsume, M.; Onaka, T.; Uchimaru, F.; Shimizu, M., *Chem. Pharm. Bull. (Tokyo)*, **14**, 672 (1966).
7. Inubushi, Y.; Tsuda, Y.; Katarao, E., *Chem. Pharm. Bull. (Tokyo)*, **14**, 668 (1966).
8. Inubushi, Y.; Nakano, J., *Tetrahedron Lett.*, 2733 (1965).
9. Conroy, H., *J. Am. Chem. Soc.*, **73**, 1889 (1951).
10. Okuda, T.; Yoshida, T., *Tetrahedron Lett.*, 2137 (1965).
11. Chen, K. K.; Chen, A. L., *J. Biol. Chem.*, **11**, 653 (1935).
12. Torssell, K. B. G. in *Natural Product Chemistry,* John Wiley and Sons Ltd., Great Britian, 1983, p. 310.
13. Inubushi, Y.; Kikushi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K., *J. Chem. Soc., Chem. Commun.*, 1252 (1972).
14. Inubushi, Y.; Kikushi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K., *Chem. Pharm. Bull.*, **22**, 349 (1974).

15. Yamada, K.; Suzuki, M.; Hayakawa, Y.; Aoki, K.; Nakamura, H.; Nagase, H.; Hirata, Y., *J. Am. Chem. Soc.*, **94**, 8279 (1972).

16. Kende, A. S.; Bently, T. J.; Mader, R. A.; Ridge, D., *J. Am. Chem. Soc.*, **22**, 349 (1974).

17. Roush, W. R., *J. Am. Chem. Soc.*, **100**, 3599 (1978).

18. Roush, W. R., *J. Am. Chem. Soc.*, **102**, 1390 (1980).

19. Martin, S. F., *J. Org. Chem.*, **54**, 265 (1989).

20. Heathcock, C. H.; Connolly, P. J., *J. Org. Chem.*, **50**, 4135 (1985).

21. Yamamoto, K.; Kawasaki, I.; Kaneko, T., *Tetrahedron Lett.*, 4859 (1970).

22. Borch, R. F.; Evans, A. J.; Wade, J. J., *J. Am. Chem. Soc.*, **97**, 6282 (1975).

23. Liu, H. J.; Ogino, T., *Tetrahedron Lett.*, 4937 (1973).

24. Nelson, L. A. K., Ph. D, University of Alberta, 1986.

25. Liu, H. J.; Nyangulu, J., *Tetrahedron Lett.*, **29**, 3167 (1988).

26. Curtis, R. G.; Heibron, S. I.; Jones, E. R. H. ; Woods, G., F., *J. Chem. Soc.*, 457 (1953).

27. Birch, A. J., *J. Chem. Soc.*, 430 (1944).

28. Yanagiya, M.; Kaneko, K.; Kaji, T.; Matsumoto, T., *Tetrahedron Lett.*, 1761 (1979).

29. Van Audenhove, M.; Dekeukeleire, D.; Vandewalle, M. *Tetrahedron Lett.*, 1979 (1980).

30. Eaton, P. E., *Tetrahedron Lett.*, 3995 (1964).

31. Corey, E. J.; La Mahieu, R.; Bass, J. D.; Mitra, R. B., *J. Am. Chem. Soc.*, **86**, 5570 (1964).

32. Demarco, P. V.; Farkas, D. D.; Mylari, B. L.; Wenkert, E., *J. Am. Chem. Soc.*, **90**, 5480 (1968).

33. Nishiguchi, T.; Machida, N.; Yamamoto, E., *Tetrahedron Lett.*, **28**, 4565 (1987).

34. Liu, H. J.; Ngooi, T. K., *Can. J. Chem.*, **62**, 2676 (1984).

35. Bohlmann, F., *Phytochemistry*, **19**, 2399 (1980).

36. Paquette, L. A.; Roberts, R. A.; Drtina, G. J., *J. Am. Chem. Soc.*, **106**, 6690 (1984).

37. Umbreit, M. A.; Sharpless, K. B., *J. Am. Chem. Soc.*, **99**, 5526 (1977).

38. Mancuso, A. J.; Huang, S.-L.; Swern, D., *J. Org. Chem.*, **43**, 2480 (1978).

39. Corey, E. J.; Burk, R. M., *Tetrahedron Lett.*, **28**, 6413 (1987).

40. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B., *J. Org. Chem.*, **46**, 3936 (1981).

41. Krow, G. R., *Tetrahedron*, **43**, 3 (1987).

42. Bellus, D.; Ernst, B., *Angew. Chem. Int. Ed. Engl.*, **27**, 797 (1988).

43. Hwang, C.-S.; Reusch, W., *Heterocycles*, **25**, 589 (1987).

44. Hwang, C.-S.; Ward, D. L.; Reusch, W., *J. Org. Chem.*, **54**, 4318 (1989).

45. Trost, B.; Latimer, L. H., *J. Org. Chem.*, **43**, 1031 (1978).

46. Lewis, F. D.; Hirsch, R. H., *Mol. Photochem.*, **2**, 259 (1970).

47. Luo, W., Personal communication.

48. Corey, E. J.; Chaykovsly, M., *J. Am. Chem. Soc.*, **87**, 1353 (1965).

49. Johnson, C. R.; Cheer, C. J.; Goldsmith, D. J., *J. Org. Chem.*, **29**, 3320 (1964).

50. Johnson, C. J.; Herr, R. W., *J. Org. Chem.*, **38**, 3153 (1973).

51. Corey, E. J.; Hertler, W. R., *J. Am. Chem. Soc.*, **82**, 1657 (1960).

52. Still, W.J.; Kahn, M.; Mitra, A., *J. Org. Chem.*, **43**, 2923 (1978).

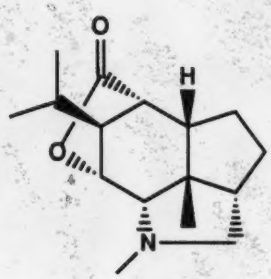
53. Windholz, M., Editor, *The Merck Index, 9th Edition*, Merck and Co., Inc., Rahway, N.J., 1976, p. 972.

CHAPTER II

APPLICATION OF THIOL ESTERS IN ORGANIC SYNTHESIS

PART I: WADSWORTH-EMMONS REACTION

INTRODUCTION



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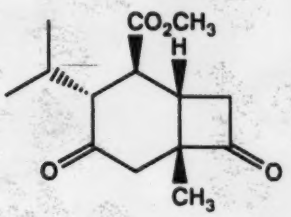
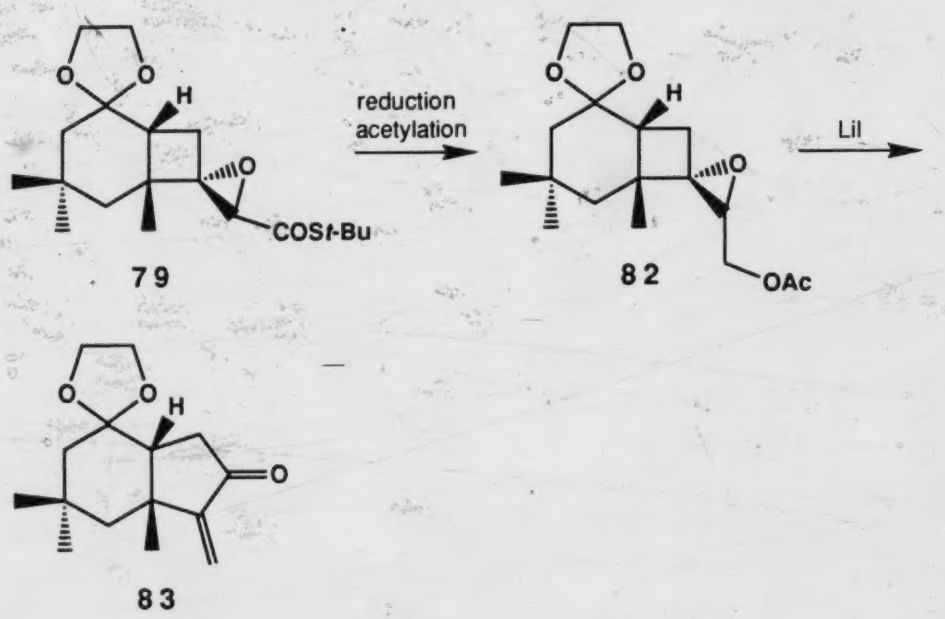


56

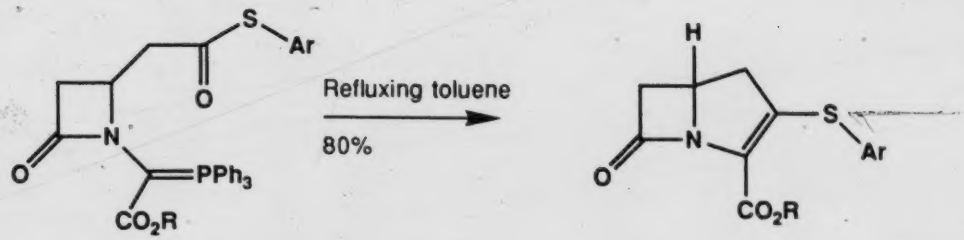
During the course of our studies on the synthesis of dendrobine **1**, we were investigating the expansion of a spiroannelated cyclobutane ring with lithium iodide, a method developed by Trost and Latimer.[1] We extended their methodology by appending an acetylated methyl group to the spirooxirane **82** in order to introduce an *exo*-methylene group into the final product **83** (see Equation 14). Thiol ester **79**, generated *via* a thiol ester analogue of the Darzens reaction, was used in this model route as we needed to differentiate between the epoxy ester from the oxygen ester present in compound **56**, which was required for the synthetic work on dendrobine. Compound **79** could be reduced and acetylated to form the epoxy acetate **82**, which was successfully ring expanded to form compound **83**. The Darzens reaction used to form compound **79**, however, was inconsistent and low yielding. Therefore, the idea of using a Wittig reagent to form an α,β-unsaturated thiol ester and subsequent functionalization to the epoxide was investigated. As it turned out, this

route towards dendrobine was eventually abandoned, with the full discussion of results being contained in Chapter I. However, some interesting methodology was developed and is discussed in this section.



Eq. 14

Previously, thiol esters have been given both electrophilic and nucleophilic roles in Wittig reactions. A classic example of the former is the intramolecular Wittig reaction in the synthesis of olivanic acid analogues by R. J. Ponsford (see Equation 15).[2] In this example, an internal Wittig reagent is attacking a thiol ester, a definitely undesirable side reaction for our intended methodology. Fortunately, a review of known Wittig reagents which contained thiol esters suggested this would not be a competing side reaction. The reagents which have been investigated previously are described below.

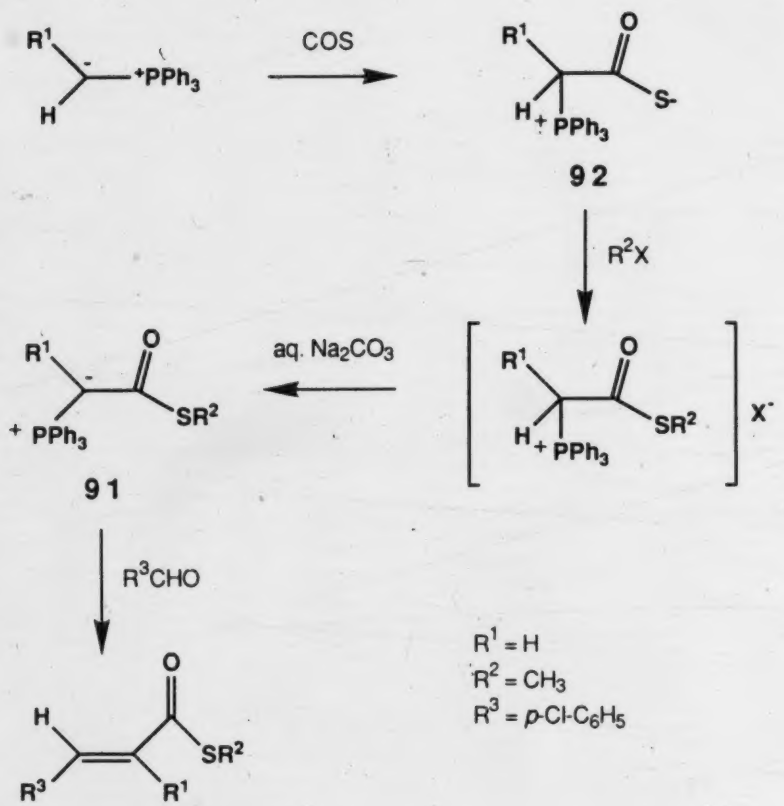


Eq. 15

The first thiol ester containing reagent was reported in 1970 by Dale and Froyen.[3] They were investigating the internal rotation of various ylides, one of them being $Ph_3PCHCOSEt$. However, no studies of their reactivity towards aldehydes and ketones were undertaken.

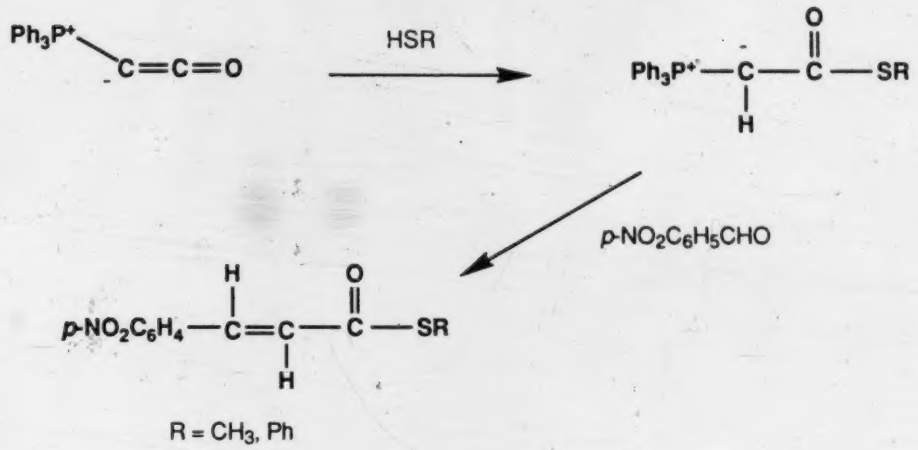
In 1979, Bestmann formed the ylid **91** *in situ* from the reaction of triphenylphosphoranes with COS to form the betaines **92** which precipitated out of solution (see Scheme 12).[4] Subsequent alkylation of the crude betaine with an alkyl halide formed the phosphonium salts, which upon treatment with aqueous sodium carbonate gave the desired ylid. The example having R_1=H, and R_2=CH_3 was shown to react with *p*-chlorobenzaldehyde in 84% yield, giving *E*-stereochemistry across the double bond. By varying the starting triphenylphosphoranes and the alkyl halide used in the second step, a wide variety of Wittig reagents could be produced.

SCHEME 12



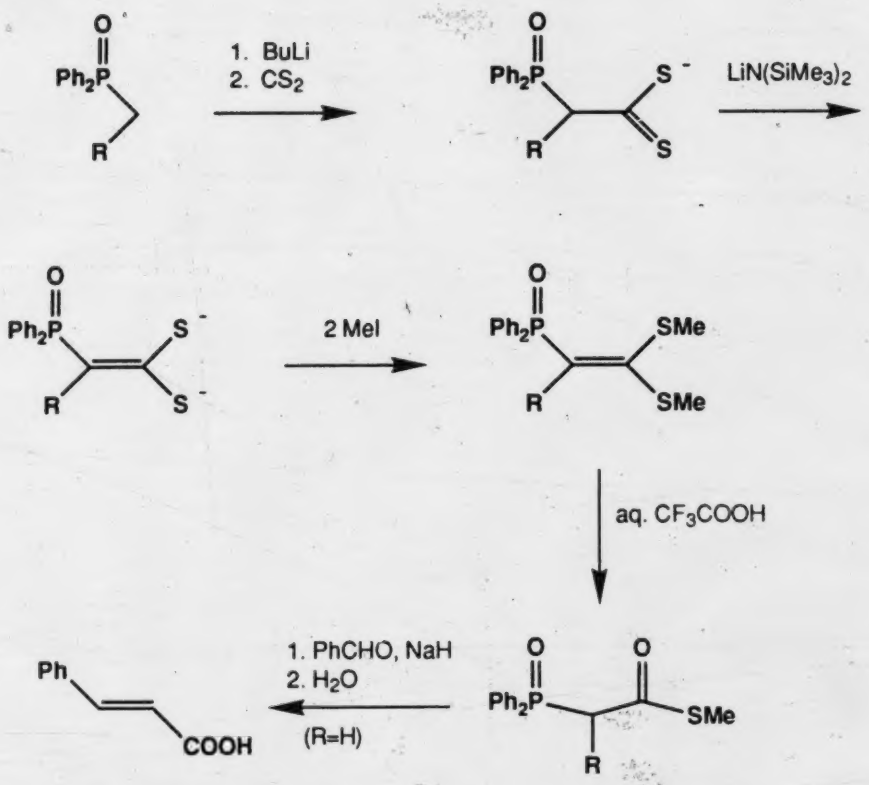
The following year, Bestmann published a second paper describing the formation of Wittig reagents (some including a thiol ester functionality) from a second class of ylides, the phosphacumulenes.[5] These reagents were generated from the phosphacumulene ylides in ~70% yield and could be reacted with *p*-nitrobenzaldehyde to form the α,β-unsaturated thiol esters (see Scheme 13).

SCHEME 13



In 1985, Schaumann described a method of forming α,β-unsaturated thiol esters using a phosphine oxide derived Wittig reagent.[6] Through their studies of the carbanions of diphenylphosphane oxides similar to the earlier work of Bestmann, they found they could easily form 2-diphenylphosphoryl ketene thioacetals by the addition of carbon disulfide to the phosphorane oxide anion and subsequent *in situ* methylation (see Scheme 14). Furthermore, the ketene thioacetals could be transformed to the *S*-thiocarboxylates by hydrolysis with aqueous trifluoroacetic acid. Reaction of the reagent having R=H with sodium hydride and benzaldehyde followed by hydrolysis gave cinnamic acid in 35% yield.

SCHEME 14

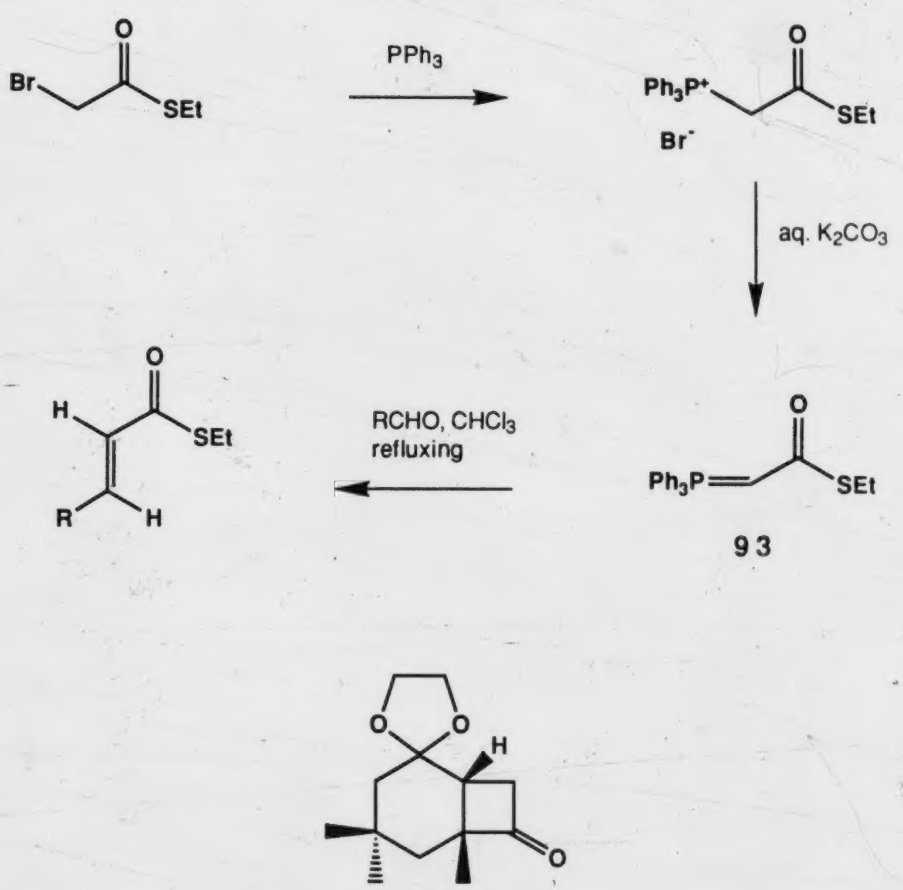


Finally, in 1985 Keck described the formation of α,β-unsaturated thiol esters of a number of base sensitive aldehydes using reagent **93**.[7] He subsequently applied the reagent to the synthesis of (+)-colletodiol.[8] The reagent was formed through reaction of *S*-ethyl bromothioacetate with triphenylphosphine and subsequent formation of the ylid using aqueous potassium carbonate in a method similar to Bestmann's (see Scheme 15).

In all cases, no reactions with ketones had been reported and in our hands application of Keck's reagent was unsuccessful with 4-*tert*-

butylcyclohexanone and 6-undecanone. Therefore, we decided to synthesize the more reactive Wadsworth-Emmons analogue, $(Et_2O)_2POCH_2COSR$, to determine if it would be reactive towards ketones, namely the model compound **74**. The following section describes the results of our efforts.

SCHEME 15



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RESULTS AND DISCUSSION

In our hands, reaction of Keck's reagent $Ph_3PCHCOSEt$ with 4-*tert*-butylcyclohexanone and 6-undecanone failed, even after extensive time in refluxing chloroform. The reagent was produced as described by Keck through reaction of *S*-ethyl bromothioacetate with triphenylphosphine to generate the bromide salt, followed by treatment with aqueous potassium carbonate to form the ylid **93** as a clear, salt-like crystal.

There was some discrepancy in the reported m.p. of the reagent (82-83°C) and the crystals we had synthesized following the reported procedure (183-184°C), and we were concerned that the ylid had not been formed during treatment with potassium carbonate. This possibility was discounted by the following ^1H NMR spectral data. The chemical shift for the hydrogen adjacent to the phosphorus atom was dramatically different for the ylid as compared to the bromide salt (δ 3.65 *vs* 5.85). The ^1H NMR spectral data for the ylid also compared favourably with that previously published by Bestmann and coworkers on a similar reagent (see Table 1),[5] leaving no doubt that the ylid had been generated.

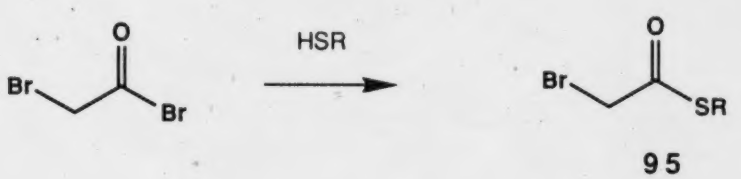
To facilitate the preparation of the α,β-unsaturated thiol ester, we decided to synthesize the more reactive Wadsworth-Emmons[9] analogue, $(EtO)_2POCH_2COSR$. Two new compounds, **84** and **94**, were prepared for this study and could be easily generated in two steps. First, reaction of 1 equivalent of bromoacetyl bromide with the appropriate alkyl mercaptan (1eq) stirring at room temperature overnight formed the *S*-alkyl bromothioacetate **95** in high yields, which could be used without further

purification. Secondly, overnight reaction of **95** with 1 equivalent of triethyl phosphite in refluxing benzene, in a typical Arbuzov reaction,[10] followed by vacuum distillation, generated reagents **84** and **94** each in approximately 90% yield (see Equation 16).

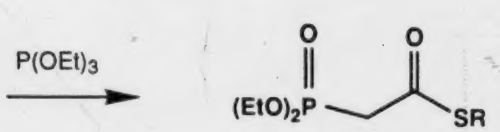
Table 1: Comparison of Chemical Shifts of Ylids

$Ph_{3A}P{=}CH_BCOSCH_{2C}R$

	A	B	C
Bestmann (R=H)	δ 7.55 (m)	δ 3.75 (d, J_{PH}=22)	δ 2.25
Keck (*vide supra*) (R=CH_3)	δ 7.55 (m)	δ 3.65 (broad d)	δ 2.85



95



84 R = $C(CH_3)_3$

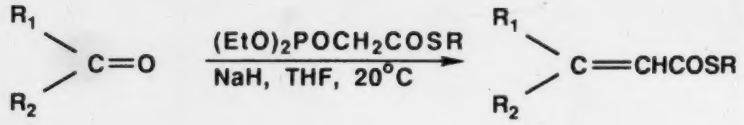
94 R = CH_2CH_3

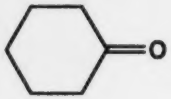
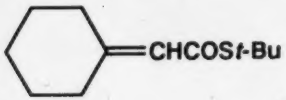
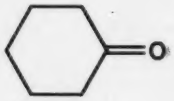
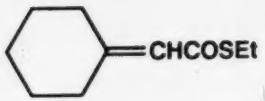
Eq. 16

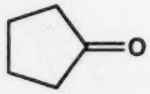
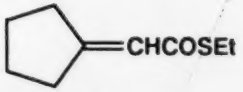
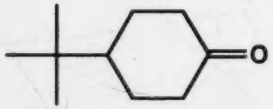
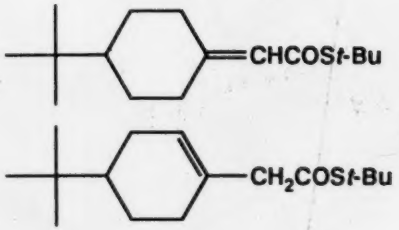
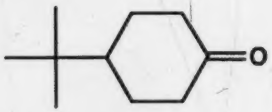
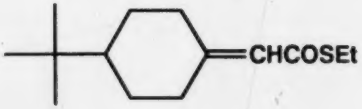
Reagent **84** showed the following spectral data. The infrared spectrum showed a strong carbonyl band at 1679 cm^{-1}, which is typical for a thiol ester. The ^1H NMR spectrum showed a peak for the nine protons on the *tert*-butyl group at δ 1.47, a peas for the ethyl group at δ 4.15 (quintet, $J = 7$ Hz (P-H and H-H), 4H) and 1.35 (t, $J = 7$ Hz, 6H) as well a doublet at δ 3.18 for the two protons adjacent to the phosphorus atom having a large P-H coupling constant of 21 Hz. HRMS gave a signal at 268.0898 for the formula $C_{10}H_{21}O_4SP$.

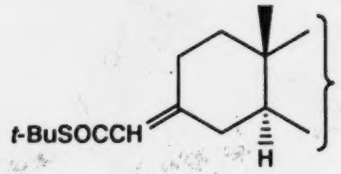
Both reagents **84** and **94** were found to undergo reaction towards aldehydes and ketones readily. A typical reaction sequence involved generating the anion by dropwise addition of a solution of the phosphonate ester (1.1-1.5 eq) in tetrahydrofuran (THF) to a stirred solution of sodium hydride (1.1-1.5 eq), under argon at 0°C. After addition, the solution was stirred for 10 minutes or until bubbling ceased and then the aldehyde or ketone (1 eq) was added. The solution was warmed to room temperature and allowed to react for about 1 hour for aldehydes while ketones required overnight (see Table 2 for a list of examples). Typical spectral data for the products include a strong carbonyl stretch between 1665 and 1670 cm^{-1}, as well as a strong carbon-carbon double bond stretch at ~1625 cm^{-1}. The ^1H NMR spectrum showed a downfield proton typically at δ 5.8-6.2 for the hydrogen on the double bond adjacent to the thiol ester. Mass spectroscopy gave a small molecular ion peak, with the 100% intensity peak usually being M-SR (R=Et or *t*-Bu). With aldehydes, the *trans* compound was the only product isolated. No *cis*

Table 2. Preparation of α,β-Unsaturated Thiol Esters

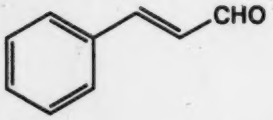


Entry	Carbonyl Compound	Phosphonate	Time (h)	Product	Isolated % Yield
1		**84**	23	 **96**	85
2§		**94**	19	 **97**	87

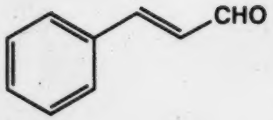
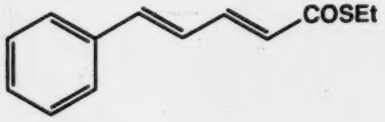
3[§]		**94**	20			80
				98		
4		**84**	17			82
				99:**100**, 5:2		
5		**94**	16			92
				101		

6	**5α-cholestan-3-one**	**84**	18		80

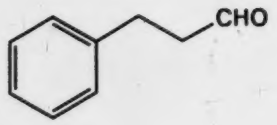
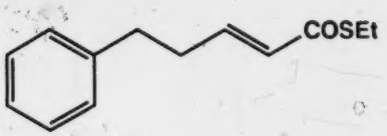
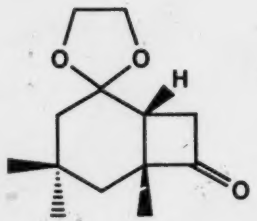
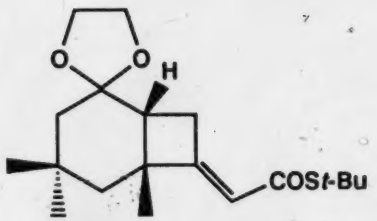
102 (2 isomers, 1:1)

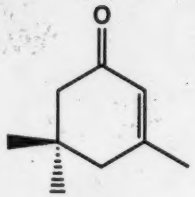
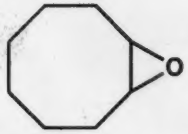
7		**84**	1		76

103

8		**94**	1		72

104

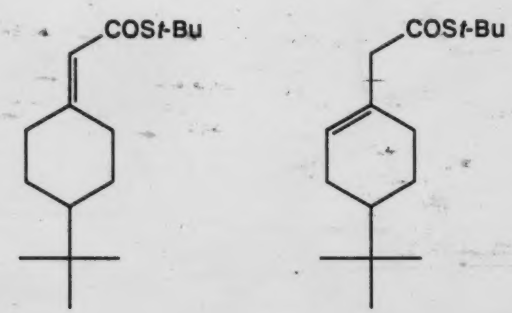
9 §		94	1			83
				105		
10	$CH_3(CH_2)_{20}CHO$	84	1.5			
				106		
11		84	24			51%
				85		

12		94	20	N.R.
13		84	24	N.R.

§ Reaction carried out by Doug Sasaki.

compound could be detected by ^{1}H NMR analysis. This result compares favourably to Keck's reagent, where the major product was also the *trans* compound, however they were able to isolate 5-20% of the *cis* compound.

Table 2 shows the ability of reagents **84** and **94** to react with aldehydes (Entries 7-10) and ketones (Entries 1-6) in high yields and with high stereoselectivity in the case of aldehydes. The reaction of 4-*tert*-butylcyclohexanone with reagent **84** (Entry 4), however, proved to be an exceptional case, forming an inseparable mixture of two compounds - the expected α,β-unsaturated thiol ester **99** as well as the corresponding β,γ-unsaturated thiol ester **100**. The latter could be distinguished by two peaks in the ^{1}H NMR, one at δ 5.35 (mt, J = 7 Hz, 1H) for the olefinic proton and the second at δ 4.15 (d, J = 7 Hz, 2H) for the two protons adjacent to the thiol ester. Also, the infrared spectrum showed two carbonyl stretches for the mixture, one at 1667 cm^{-1} for the conjugated thiol ester and the second a shoulder at ~1690 cm^{-1} for the non-conjugated thiol ester.



α,β β,γ

99 **100**

Apparently, the added steric hinderance of the *tert*-butyl group across the double bond of the exocyclic conjugated system was enough to force partial migration of the double bond into the ring. Interestingly, the reaction of 4-*tert*-butylcyclohexanone with reagent **94** (Entry 5), having the smaller ethyl thiol ester, showed only the desired product.

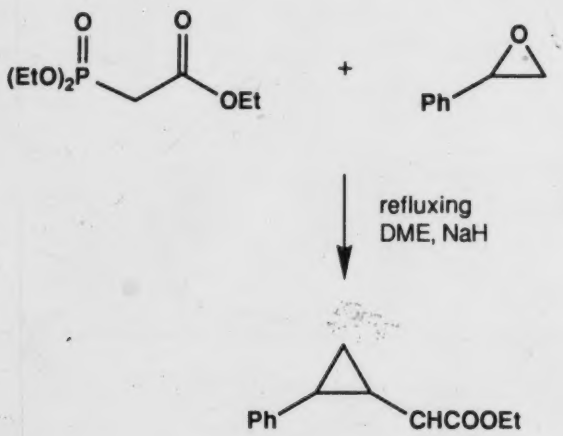
The reaction of reagent **94** with model compound **74** (Entry 11) occurred in only moderate yield. This could be explained by both the steric hinderance surrounding the cyclobutanone center, which is a neopentyl center, as well as by the fact that reforming the sp^2 center on a cyclobutane ring after inital attack of the Wadsworth-Emmons reagent is difficult due to the ring strain produced.

Reagent **94** was reacted with isophorone (Entry 12) to test its reactivity with α,β-unsaturated ketones. After a 20 hour reaction time under the described conditions, no product could be detected.

Finally, as the original Wadsworth-Emmons reagent was shown to react with epoxides to form substituted cyclopropanes (see Equation 17),[9] a model reaction was run between cyclooctene oxide and reagent **84** (Entry 13). After 24 hours under the described conditions, no product could be detected.

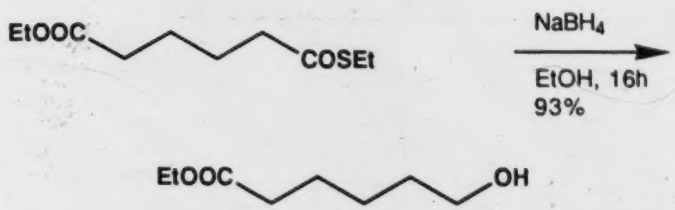
With a successful method of forming the α,β-unsaturated thiol ester **85** in hand, the next step required the development of a method to form the spiro epoxy acetate **82**. Two routes could be taken, the first being direct epoxidation to form the spiro epoxide **79**, which had been made

previously and could be reduced and acetylated to form compound **82**. Unfortunately, model reactions between compound **95** and MCPBA generated a very complex reaction mixture, and therefore a second route, involving the selective reduction of the thiol ester to the allylic alcohol (which could then be epoxidized and acetylated) was investigated.



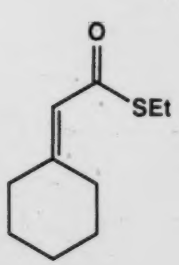
Eq. 17

A method of transforming the thiol ester to an acid while leaving the double bond intact had been demonstrated by Keck through the use of silver nitrate and lutidine.[8] We were more interested in reducing the compounds down to the allylic alcohol level. Therefore, we investigated several reducing agents which could selectivily reduce the thiol ester in the presence of oxygen esters. Initially, sodium borohydride was the reagent of choice, as it is a mild reducing agent and had been shown previously in our group to reduce saturated thiol esters selectively to the primary alcohol, even in the presence of ordinary esters (see Equation 18).[11]

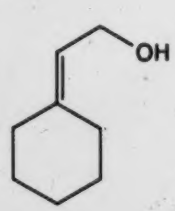


Eq. 18

Therefore, in a model reaction compound **97** was reacted with 2 equivalents of sodium borohydride in ethanol at room temperature for two days. Unfortunately, the major product from the reaction was that of transesterification with the solvent, however some allylic alcohol **107** was formed, as evidenced by the following spectral data. The infrared spectrum showed a large hydroxyl stretch centered around 3320 cm^{-1}, as well, the carbonyl band was no longer present. The ^1H NMR spectrum showed a triplet at δ 5.5 (J = 7 Hz, 1H) for the hydrogen on the double bond which was coupled to the two allylic hydrogens adjacent to the hydroxyl group (δ 4.18, d, J = 7 Hz, 2H). Mass spectroscopy showed a molecular ion peak at 126.1044.



97

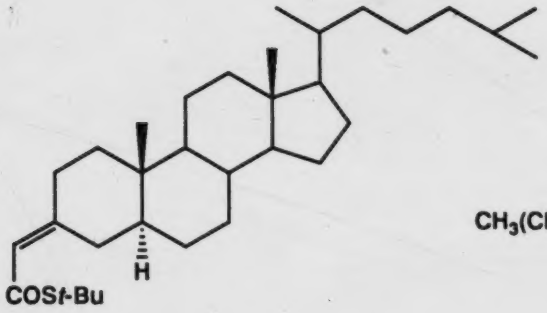


107

Under these reaction conditions, the rate of reduction was slow enough to allow the competing transesterification reaction to take over. Higher temperatures to increase the rate of reduction and bulkier solvents to block the side reaction were tried without success. Even with the use of the *tert*-butyl thiol ester **96** as the substrate and refluxing isopropanol as the solvent, transesterification was a major problem.

Lithium borohydride is known to be partially soluble in THF and is also a mild reducing agent and was our next alternative. By running the reaction in a non-nucleophilic solvent, the transesterification reaction would be eliminated. However, the reduction of **97** was very slow (> 2 days) even at refluxing temperatures and the products were an inseparable mixture of the allylic and the fully saturated alcohol. Stronger reducing agents such as lithium aluminium hydride were not investigated as they would no longer provide the required selectivity between the oxygen and thiol esters.

Raney-Nickel catalysts are known to cleave carbon-sulfur bonds, and have been shown to reduce thiol esters to the alcohol stage. Two model reactions with compounds **102** and **106** were carried out to determine if the double bond would remain intact under Raney-Nickel reduction conditions. Also, as transesterification was previously shown to be a problem, a modified procedure of forming the Raney-Nickel was utilized which involved an acid wash to remove any residual hydroxide ion.

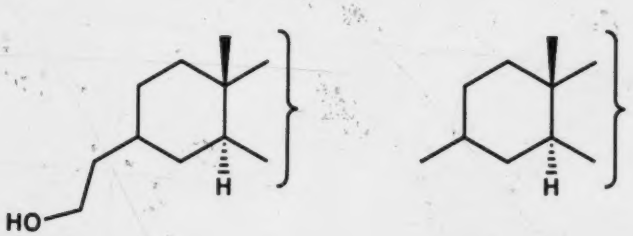


102

106

Thus, modified W2 Raney-Nickel was prepared *via* the reaction of nickel-aluminum alloy with concentrated NaOH. After washing with water, 5% acetic acid, and water again the reagent was washed and then stored under ethanol. The Raney-Nickel (1.3 mL / 100 mg) was washed with benzene (3 X 5 mL) and then added to a solution of the thiol ester in benzene and stirred for 10 minutes. Careful filtration followed by purification gave a mixture of two products for each case. For compound **102**, the major product (63%) was compound **108**, the saturated alcohol. This was substantiated by a large hydroxyl band at 3350 cm^{-1} in the infrared spectrum and a molecular ion peak in the HRMS at 414.4022 for the formula $C_{29}H_{52}O$. The proton NMR spectrum showed one set of methyl peaks typical of the cholestane skeleton. However, it also showed a peak at δ 3.75 for the protons adjacent to the hydroxyl group as an overlapping pair of triplets (J = 6.5 Hz), in a 1:1 ratio. This suggested that both the 3α and the 3β hydroxyethyl cholestane compounds had been formed. The second product, in 23% yield, was unexpected. All spectral data pointed to structure **109**, a completely saturated alkane having one less carbon than the first product described. The infrared spectrum

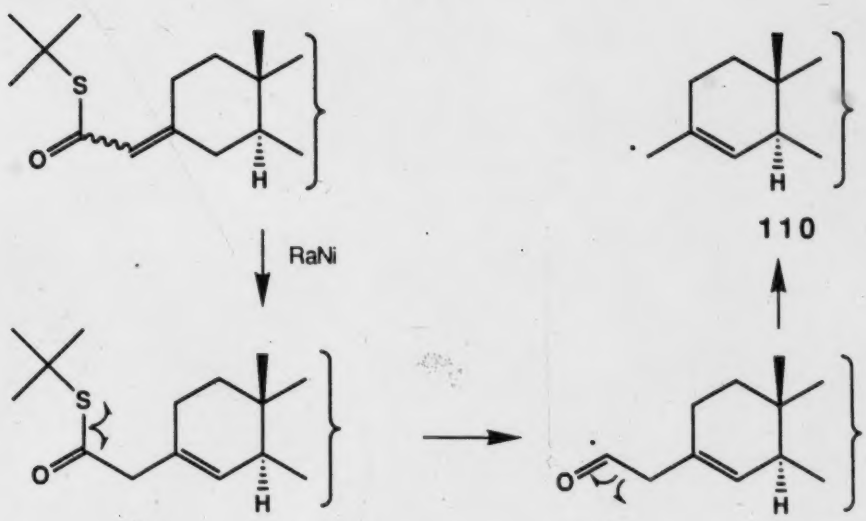
showed only C-H and C-C bond stretches. The ^1H NMR spectrum showed no peaks downfield of δ 2.0, but still showed the steroidal structure. The structural proof came from the EI mass spectrum, where the 100% peak was 386.3912 for the formula $C_{28}H_{50}$ for compound **109**.



108 **109**

The saturated alkane could be generated from an intermediate radical, **110**. This radical could form under Raney-Nickel conditions by initial migration of the double bond into the ring, followed by successive loss of the *tert*-butylthiol radical and then decarbonylation. Further hydrogenation of the allylic radical by the catalyst would provide compound **109** (see Equation 19). Similarly, compound **106** also formed a saturated alcohol and saturated alkane (44% and 49% respectively) upon reduction with Raney-Nickel.

Thiol ester analogues of the Wadsworth-Emmons reagent have been shown to be reactive towards both aldehydes and ketones in high yields and with high stereoselectivity. They provide a useful method for forming α,β-unsaturated thiol esters. The method was not found to be useful in the synthesis of dendrobine; however, some interesting chemistry was developed from the investigation of this route.



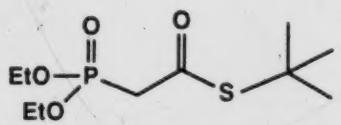
Eq. 19

EXPERIMENTAL

General and Materials

Refer to Chapter I, Experimental Section for a detailed description of general procedures and materials data.

Diethyl *tert*-butylthiocarbonylmethylphosphonate (84).

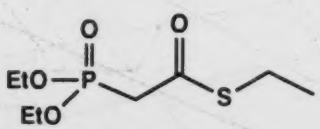


Glacial acetic acid (20 mL, 0.35 mol, 1 eq) was mixed with 9.86 mL (28.4 g, 0.10 mol, 0.3 eq,) PBr_3 in a 300 mL three-necked flask equipped with condenser, stirrer, dropping funnel and under an atmosphere of argon. The top of the condenser was connected to a KOH trap *via* a gas outlet connecting tube. The mixture was heated to 100°C and 1.5 equivalents (27.6 mL, 0.54 mol) of bromine was added over a 3 hour period, to form bromoacetyl bromide. The solution was cooled and the excess bromine was flushed out of the system with a stream of argon followed by the addition of 100 mL of CH_2Cl_2. At 0°C, *tert*-butylmercaptan (47.3 mL, 0.42 mol, 1.2 eq) was slowly added and then left for 6 hours at room temperature. At this point, water (100 mL) was added to the mixture and the layers separated. The CH_2Cl_2 layer was washed with 1N NaOH (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Further purification was

carried out by quickly washing through a short column of flash silica gel to remove the polar impurities, to yield 49.3 g (66%) of *S-tert*-butyl bromothioacetate. ^{1}H NMR showed two peaks: δ 3.94 (s, 2H, -C**H**$_2$) and 1.5 (s, 9H, -C(C**H**$_3$)$_3$). FTIR: 1691 (C=O) cm^{-1}. HRMS M$^+$: 211.9698 and 209.9715 (calcd. for $C_6H_{11}SOBr$ 211.9698 and 209.9714).

The Wadsworth-Emmons reagent was then formed by mixing 28.4 g (0.135 mol) of the α-bromo thiol ester with 1 equivalent (23.3 mL, 0.135 mol) of triethyl phosphite at room temperature, followed by heating to reflux and stirring for 24 hours. Distillation under reduced pressure (147-149°C at 3.6 mm Hg) afforded the desired product **84** in 89% yield (31.1 g). ^{1}H NMR (400 MHz): δ 4.15 (quintet, J = 7.5(P-H and H-H) Hz, 4H, -OC**H**$_2$), 3.13 (d, J = 21(H-P) Hz, 2H, -PC**H**$_2$), 1.47 (s, 9H, -C(C**H**$_3$)$_3$), 1.30 (t, J = 7 Hz, 6H, 2 X -C**H**$_3$). ^{13}C NMR (100 MHz): δ 191 (**C**=O), 62 (O**C**H), 49.5, 44.5, 43, 29 (-C(**C**H$_3$)$_3$), 16. FTIR: 1679 (C=O), 1263 (P=O) cm^{-1}. HRMS M$^+$: 268.0898 (calcd. for $C_{10}H_{21}PO_4S$ 268.0898).

Diethyl ethylthiocarbonylmethylphosphonate (94).



Bromoacetyl bromide (10 mmol, 0.87 mL) was dissolved in 20 mL of CH_2Cl_2 and cooled to 0°C. Ethyl mercaptan (10 mmol, 0.74 mL) dissolved in 5 mL of CH_2Cl_2 was added dropwise. After addition, the solution was warmed to room temperature and left to stir overnight. The CH_2Cl_2 was then washed with a 5% sodium carbonate solution (2 X 25 mL), water (2 X

25 mL) and brine (25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. This afforded ~2 g of crude product which could be used without further purification. The Wadsworth-Emmons reagent was then formed by mixing 10 mmol (1.72 mL) of triethyl phosphite with the crude product in 10 mL benzene at room temperature, followed by heating to reflux and stirring for 24 hour. Distillation under reduced pressure(114-116 °C at 0.6 mm Hg) afforded the desired product **94** in 91% yield (2.19 g). ^{1}H NMR (200 MHz): δ 4.16 (quintet, J = 7.5(P-H and H-H) Hz, 2H, -OC**H**$_2$), 3.20 (d, J = 21(H-P), 2H, -PC**H**$_2$), 2.92 (q, J = 7 Hz, 2H, -SC**H**$_2$CH$_3$), 1.34 (t, J = 7.5 Hz, 6H, -OCH$_2$C**H**$_3$), 1.26 (t, J = 7 Hz, 3H, -SCH$_2$C**H**$_3$). FTIR: 1684 (C=O), 1262 (C-S), 1025 (C-O) cm^{-1}. HRMS M$^+$: 240.0582 (calcd. for $C_8H_{17}PO_4S$ 240.0585).

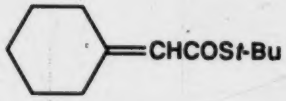
General procedure for forming the α,β-unsaturated thiol ester

The following procedure was used for forming all the α,β-unsatured thiol esters in this section, based on approximately a 1 mmol scale.

To a dried 50 mL three-necked flask containing 1 mL of THF was added 1.1-1.5 equivalents of sodium hydride (60% dispersion in oil). This was cooled to 0°C, with stirring, and 1.1-1.5 equivalents of the Wadsworth-Emmons reagent **84** or **94** in 0.5 mL of THF was slowly added . The mixture was stirred for 10 minutes, or until bubbling ceased, indicating complete formation of the anion. The carbonyl compound (1 eq in 0.5 mL THF) was added and the mixture warmed to room temperature. After disappearance of the carbonyl compound by TLC (typically 1 hour for aldehydes and overnight for ketones) the mixture was quenched with 10

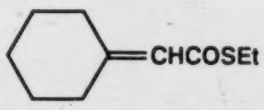
mL of 1M HCl, extracted into CH_2Cl_2 (3 X 20 mL) and the combined organic extracts washed with 20 mL of brine, then dried over magnesium sulfate, filtered and concentrated. Flash silica gel chromatography was used to purify the newly formed, non-polar compounds.

(*tert*-Butylthio)carbonylmethylenecyclohexane (96).



Following the general procedure, 1.0 mmol (1 eq, 111 mg) of freshly distilled cyclohexanone was reacted with 1.1 mmol (1.1 eq, 42 mg) of NaH and 1.1 mmol (1.1 eq, 287 mg) of reagent **84**. After workup and flash chromatography (20% ether / petroleum ether), 186 mg (86%) of an amorphous solid was isolated. ^{1}H NMR (200 MHz): δ 5.84 (t, J = 1 Hz, 1H, =C**H**), 2.78 (m, 2H, =CC**H**$_2$), 2.14 (m, 2H, =CC**H**$_2$), 1.62 (m, 6H, -C**H**$_2$C**H**$_2$C**H**$_2$), 1.47 (s, 9H, -C(C**H**$_3$)$_3$). FTIR: 1664 (C=O), 1623 (C=C) cm^{-1}. HRMS M$^+$: 212.1221 (calcd. for $C_{12}H_{20}OS$ 212.1235).

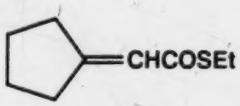
(Ethylthio)carbonylmethylenecyclohexane (97).



Following the general procedure, 1.0 mmol (1.0 eq, 98 mg) of freshly distilled cyclohexanone was reacted with 1.5 mmol (1.5 eq, 39 mg) of NaH and 1.5 mmol (1.5 eq, 390 mg) of reagent **94**. After workup and flash chromatography (10% ether / petroleum ether), 161 mg (87%) of a clear oil

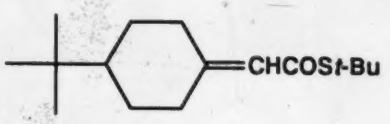
was isolated. ^{1}H NMR (200 MHz): δ 5.86 (s, 1H, =C**H**), 2.89 (q, *J* = 7 Hz, 2H, -C**H**$_2$CH$_3$), 2.78 (m, 2H, =CC**H**$_2$), 2.14 (m, 2H, =CC**H**$_2$), 1.62 (m, 6H, -C**H**$_2$C**H**$_2$C**H**$_2$), 1.28 (t, *J* = 7 Hz, 3H, -CH$_2$C**H**$_3$). FTIR: 1668 (C=O), 1624 (C=C) cm^{-1}. HRMS M$^+$: 184.0921 (calcd. for $C_{10}H_{16}OS$ 184.0922). Anal. Calcd. for $C_{10}H_{16}OS$: C, 65.17; H, 8.75; S, 17.40. Found: C, 65.04; H, 8.96; S, 17.28.

(Ethylthio)carbonylmethylenecyclopentane (98).

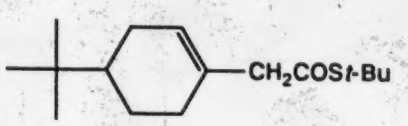


Following the general procedure, 2.0 mmol (1 eq, 168 mg) of freshly distilled cyclopentanone was reacted with 2.6 mmol (1.3 eq, 125 mg) of NaH and 2.6 mmol (1.3 eq, 617 mg) of reagent **94.** After workup and flash chromatography (10% ether / petroleum ether), 245 mg (70%) of the desired product was isolated, along with 19.5 mg of recovered starting material, bringing the yield to 80% (based on recovered starting material). ^{1}H NMR (200 MHz): δ 6.10 (t, *J* = 2Hz, 1H, =C**H**), 2.90 (q, *J* = 7 Hz, 2H, -C**H**$_2$CH$_3$), 2.74 (m, 2H, =CC**H**$_2$), 2.38 (m, 2H, =CC**H**$_2$), 1.70 (m, 4H, -C**H**$_2$C**H**$_2$), 1.25 (t, *J* = 7 Hz, 3H, -CH$_2$C**H**$_3$). FTIR: 1667 (C=O), 1626 (C=C) cm^{-1}. HRMS M$^+$: 170.0765 (calcd. for $C_9H_{14}OS$ 170.0765).

4-*tert*-Butyl-(*tert*-butylthio)carbonylmethylenecyclohexane (99) and 4-*tert*-Butyl-1-(*tert*-butylthio)carbonylmethylcyclohexene (100).



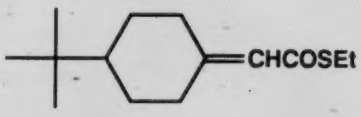
99



100

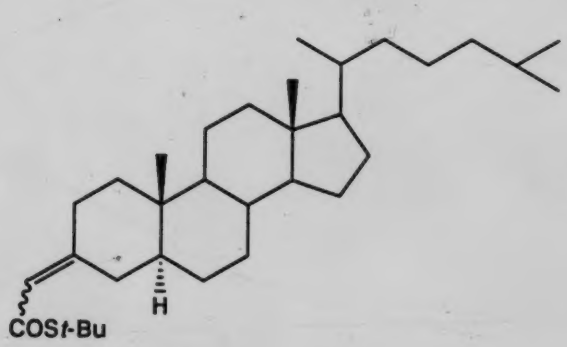
Following the general procedure, 2.0 mmol (1 eq, 309 mg) of *tert*-butylcyclohexanone was reacted with 2.2 mmol (1.1 eq, 63 mg) of NaH and 2.2 mmol (1.1 eq, 573 mg) of reagent **84**. After workup and flash chromatography (25% ether / petroleum ether), 435 mg (82%) of a clear oil was isolated as an inseparable mixture of α,β– and β,γ-isomers (2:1 ratio). The mixture showed the following spectral data. FTIR: 1680 (shoulder, C=O), 1667 (unsaturated thiol ester C=O), 1625 (C=C) cm^{-1}. HRMS M+: 268.1858 (calcd. for $C_{16}H_{28}OS$ 268.1861). The ^1H NMR (400 MHz) spectrum showed the following signals for the major isomer: δ 5.51 (m, 1H, -C=C**H**COSR), 3.65 (m, 2H, =CC**H**$_2$), 2.20 (t, J = 6 Hz, 2H, =CC**H**$_2$), 0.83 (s, 18H, -C(C**H**$_3$)$_3$). The minor isomer showed the following peaks in the ^1H NMR (400 MHz) spectrum: δ 5.35 (tt, J = 2, 7 Hz, 1H, -C**H**=CCH$_2$COSR), 4.15 (d, J = 7 Hz, 2H, -C**H**$_2$COSR), 3.65 (m, 2H, =CC**H**$_2$), 0.85 (s, 9H, -C(C**H**$_3$)$_3$), 0.87 (s, 9H, -C(C**H**$_3$)$_3$).

4-*tert*-Butyl-(ethylthio)carbonylmethylenecyclohexane (101).



Following the general procedure, 1.0 mmol (1.0 eq, 150 mg) of *tert*-butylcyclohexanone was reacted with 1.5 mmol (1.5 eq, 72 mg) of NaH and 1.5 mmol (1.5 eq, 400 mg) of reagent **94**. After workup and flash chromatography (10% ether / petroleum ether), 214 mg (92%) of a clear oil was isolated. ^{1}H NMR (200 MHz): δ 5.86 (s, 1H, =C**H**), 3.80 (m, 1H, =CC**H**), 2.88 (q, *J* = 7 Hz, 2H, -SC**H**$_2$CH$_3$), 2.20 (m, 2H, =CC**H**$_2$), 1.90 (m, 3H), 1.25 (t, *J* = 7 Hz, 3H, -SCH$_2$C**H**$_3$ overlapping with m, 3H). FTIR: 1671 (C=O), 1627 (C=C) cm^{-1}. HRMS M$^+$: 240.1539 (calcd. for $C_{14}H_{24}OS$ 240.1548). Anal. Calcd. for $C_{14}H_{24}OS$: C, 69.95; H, 10.06; S, 13.34. Found: C, 70.10; H, 10.16; S, 13.23.

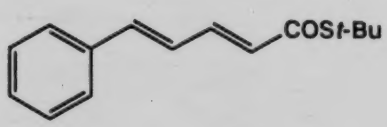
3-(*tert*-Butylthio)carbonylmethylene-5α-cholestane (102).



Following the general procedure, 1.0 mmol (1.0 eq, 397 mg) of 5α-cholestane-3-one was reacted with 1.5 mmol (1.5 eq, 46 mg) of NaH and 1.5 mmol (1.5 eq, 372 mg) of reagent **84**. After workup and flash

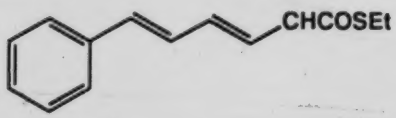
chromatography (10% ether / petroleum ether), 410 mg (80%) of a clear oil was isolated along with 45 mg (11%) of unreacted starting material. The product was an inseparable mixture of E and Z isomers present in a 1:1 ratio. ^{1}H NMR (400 MHz): δ 5.80 (s, 0.5H, =C**H**), 5.82 (s, 0.5H, =C**H**), 1.50 (s, 9H, -C(C**H**$_3$)$_3$), 0.95 (s, 3H, -C**H**$_3$), 0.90 (d, *J* = 6 Hz, 3H, -CHC**H**$_3$), 0.86 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)$_2$), 0.84 (d, *J* = 6 Hz, 3H, -CH(C**H**$_3$)$_2$), 0.65 (s, 3H, -C**H**$_3$). FTIR: 1667 (C=O), 1622 (C=C) cm^{-1}. HRMS M$^+$: 500.4050 (calcd. for $C_{33}H_{56}OS$ 500.4052).

***S-tert*-Butyl 5-phenyl-2*E*,4*E*-pentadienethioate (103).**



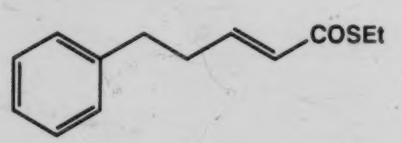
Following the general procedure, 2.0 mmol (1 eq, 264 mg) of freshly distilled cinnamaldehyde was reacted with 2.2 mmol (1.1 eq, 88 mg) of NaH and 3 mmol (1.5 eq, 720 mg) of reagent **84**. An excess of base was avoided due to the base sensitivity of this aldehyde. After workup and flash chromatography (10% ether / petroleum ether), 376 mg (76%) of a yellow oil was isolated. ^{1}H NMR (200 MHz): δ 7.2-7.5 (m, 6H, Ar and -C**H**=), 6.85 (d, *J* = 15, Hz, 1H, Ar-C**H**=), 6.80 (dd, *J* = 15, 10 Hz, 1H, Ar-CH=C**H**-), 6.20 (d, *J* = 15 Hz, 1H, =C**H**-CO), 1.52 (s, 9H, -C(C**H**$_3$)$_3$). FTIR (CH_2Cl_2 cast): 1662 (C=O), 1621 (C=C) cm^{-1}. HRMS M$^+$: 246.1078 (calcd. for $C_{15}H_{18}OS$ 246.1078).

S-Ethyl 5-phenyl-2*E*,4*E*-pentadienethioate (104).



Following the general procedure, 1.0 mmol (1 eq, 136 mg) of freshly distilled cinnamaldehyde was reacted with 1.5 mmol (1.5 eq, 60 mg) of NaH and 1.5 mmol (1.5 eq, 363 mg) of reagent **94**. After workup and flash chromatography (5% ether / petroleum ether), 161 mg (72%) of known compound **104**[7] was isolated. ^{1}H NMR (200 MHz): δ 7.4 (m, 6H, Ar and -C**H**=), 6.96 (d, *J* = 15, Hz, 1H, Ar-C**H**=), 6.80 (dd, *J* = 15, 10 Hz, 1H, Ar-CH=C**H**-), 6.28 (d, *J* = 15 Hz, 1H, =C**H**-CO), 2.98 (q, *J* = 7 Hz, 2H, -SC**H**$_2$CH$_3$), 1.28 (t, *J* = 7 Hz, 3H, -SCH$_2$C**H**$_3$). FTIR: 1668 (C=O), 1659 (C=C) cm^{-1}. HRMS M$^+$: 218.0766 (calcd. for $C_{13}H_{14}OS$ 218.0765).

S-Ethyl 5-phenyl-2*E*-pentenethioate (105).



Following the general procedure, 1.0 mmol (1 eq, 137 mg) of freshly distilled dihydrocinnamaldehyde was reacted with 1.3 mmol (1.3 eq, 41 mg) of NaH and 1.3 mmol (1.3 eq, 317 mg) of reagent **94**. After workup and flash chromatography (5% ether / petroleum ether), 194 mg (83%) of a clear oil was isolated. ^{1}H NMR (200 MHz): δ 7.3 (m, 5H, Ar), 6.94 (dt, *J* = 15.5, 6.5, Hz, 1H, -C**H**=CHCO), 6.15 (dt, *J* = 15.5, 1.5 Hz, 1H, =C**H**CO), 2.95 (q, *J* = 7 Hz, 2H, -SC**H**$_2$CH$_3$), 2.78 (m, 2H, Ar-C**H**$_2$), 2.48 (m, 2H,

-CH_2CH), 1.26 (t, J = 7 Hz, 3H, -SCH_2CH_3). FTIR: 1672 (C=O), 1632 (C=C) cm^{-1}. HRMS M^+: 220.0923 (calcd. for $C_{13}H_{16}OS$ 220.0922).

S-tert-Butyl-2_E_-tetracosenethioate (106).

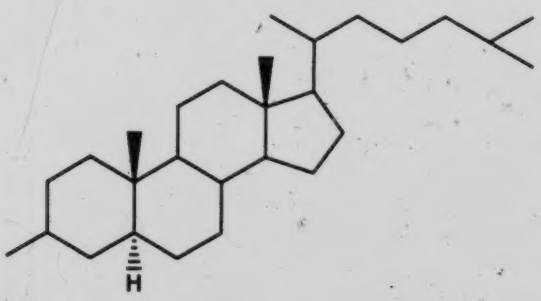
Following the general procedure, 0.43 mmol (1 eq, 138 mg) of 1-docosonaldehyde was reacted with 0.45 mmol (1.1 eq, 15 mg) of NaH and 0.45 mmol (1.1 eq, 114 mg) of reagent **84**. After workup and flash chromatography (5% ether / petroleum ether), 168 mg (92%) of a clear oil was isolated. ^1H NMR (400 MHz): δ 6.84 (dt, J = 15, 7 Hz, 1H, -C**H**=), 6.02 (dt, J = 15, 1.5 Hz, 1H, =C**H**-CO), 2.16 (dq, J = 7, 1.5 Hz, 2H, -CH_2CH=), 1.50 (s, 9H, -$C(CH_3)_3$), 1.3 (m, 38H), 0.88 (vt, J = 7 Hz, 3H, -CH_3). FTIR: 1672 (C=O), 1631 (C=C) cm^{-1}. HRMS M^+: 438.3889 (calcd. for $C_{28}H_{54}OS$ 438.3895).

Preparation of Modified W-2 Raney-Nickel

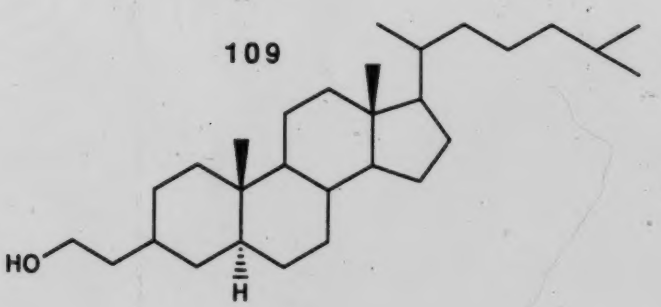
In a 1 L Erlenmeyer flask, 76 g of sodium hydroxide was dissolved in 300 mL of distilled water. The solution was cooled to 0°C and 15 g of nickel-aluminium alloy slowly added with stirring at such a rate as to keep the temperature of the solution below 25°C. If the addition of the alloy is too fast, the H_2 evolution is too rapid to control. When the evolution of gas had slowed down, the solution was warmed to room temperature and then heated on a steam bath for ~6 hours, or until H_2 evolution had almost ceased. The solvent was decanted and the residue washed with distilled

water (2 X 200 mL). At no time should the Raney-Nickel be allowed to dry out as it is highly pyrophoric. 100 ML of 10% sodium hydroxide solution was added and the solution stirred for a further 10 minutes. Decant, then wash successively with: 4 X 200 mL distilled water, 2 X 200 mL of 0.005 M acetic acid, 4 X 200 mL of water, and then 3 X 80 mL of ethanol. The Raney-Nickel can be safely stored under ethanol in a well sealed container. The activity does decrease with time.

3-Methyl-5α-cholestane (109) and 3-Hydroxyethyl-5α-cholestane (108).



109



108

Compound **102** (228 mg) was dissolved in 2 mL of benzene. Acid washed W-2 Raney-Nickel (3 mL, settled volume) was added in 3 mL of benzene. Typically, 1.3 mL of Raney-Nickel / 100 mg of compound was employed. The mixture was stirred for 10 minutes at room temperature at

which time thin layer chromatography indicated the disappearance of all starting material. The mixture was carefully filtered and washed well with dichloromethane. The organics were concentrated and subjected to flash silical gel chromatography (25% ether / petroleum ether). The first compound off the column was alkane **109**, as a clear oil, 40.6 mg (23%). ^{1}H NMR (400 MHz): δ 0.94 (d, J = 4 Hz, 3H), 0.91 (d overlapping with a m, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.87 (d, J = 1.5 Hz, 3H), 0.85 (d, J = 1.5 Hz, 3H), 0.68 (s, 3H). FTIR: 2927 (C-H), 2865 (C-H), 1466 and 1455 (C-H) cm^{-1}. HRMS M$^+$: 386.3912 (calcd. for $C_{28}H_{50}$ 386.3912). Further elution gave alcohol **108** in 63% yield (119 mg) as a white solid (m. p. = 89-91°C), as a 1:1 mixture of α and β isomers. ^{1}H NMR (400 MHz): δ 3.75 (two overlapping triplets, 2H, -C**H**$_2$OH), 0.94 (s, 3H, -C**H**$_3$), 0.90 (d, 3H, -CHC**H**$_3$), 0.87 (d, J = 2 Hz, 3H, -CH(C**H**$_3$)$_2$), 0.85 (d, J = 2 Hz, 3H, -CH(C**H**$_3$)$_2$), 0.65 (s, 3H, -C**H**$_3$). FTIR: 3350 (O-H), 2929 (C-H) cm^{-1}. HRMS M$^+$: 416.4022 (calcd. for $C_{29}H_{52}O$ 416.4018).

Tricosane and 1-Tetracosanol

Following the above procedure, 147.5 mg of thiol ester **106** was dissolved in 4 mL benzene and reacted with 1.5 mL Raney-Nickel for 10 minutes. After workup and flash chromatography, 53 mg (44% yield) of the known compound tricosane[22] was isolated as an oil. ^{1}H NMR (400 MHz): δ 1.28 (bs, 42H, -C**H**$_2$-), 0.92 (vt, J = 7 Hz, 6H, -C**H**$_3$). FTIR ($CHCl_3$/MeOH cast): 2917 (C-H), 2849 (C-H) cm^{-1}. HRMS M$^+$: 324.3756 (calcd. for $C_{23}H_{48}$ 324.3756). Further elution produced 1-tetracosanol in 49% yield (52 mg) as a white crystal, m.p. = 64-66°C. ^{1}H NMR (400 MHz): δ 3.65 (t, J = 7 Hz, 2H, -C**H**$_2$-OH), 1.58 (quintet, J = 7 Hz, 2H, -C**H**$_2$C**H**$_2$OH), 1.26 (s, 43H,

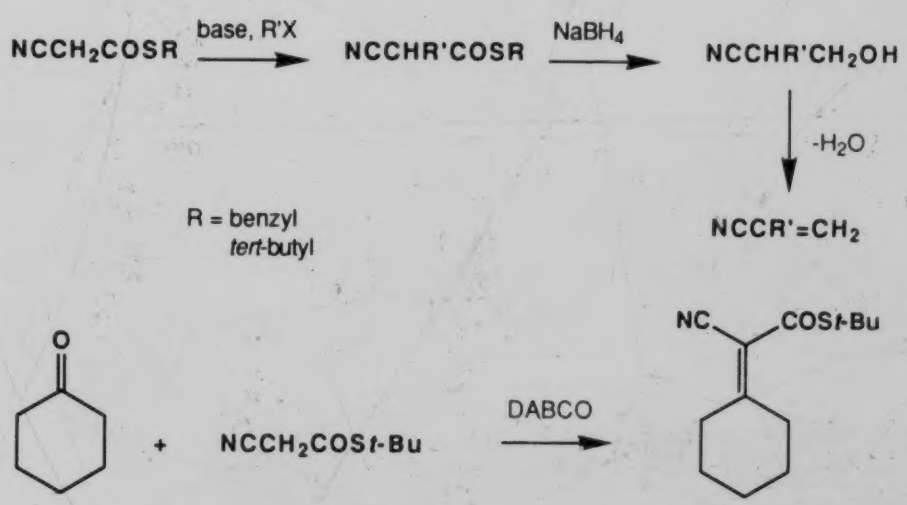
-CH_2), 0.59 (vt, J = 7 Hz, 3H, -CH_3). FTIR: 3250 (O-H), 2916 (C-H), 2848 (C-H) cm^{-1}. HRMS $(M - H_2O)^+$: 336.3758 (calcd. for $C_{24}H_{48}$ 336.3756).

PART II: KNOEVENAGEL CONDENSATION

INTRODUCTION

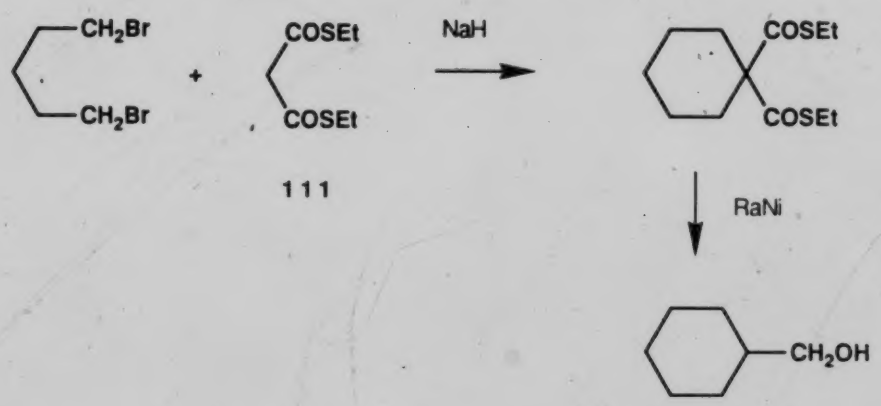
The Knoevenagel condensation has been a widely used method in organic synthesis for many years. It involves the condensation of an aldehyde or ketone with compounds of the type $Z\text{-}CH_2\text{-}Z$ or $Z\text{-}CH_2\text{-}Z'$, where Z and Z' are electron withdrawing groups such as CHO, COR, CO_2H, CO_2R, CN, NO_2, SOR, SO_2R, SO_2OR etc.[12]

Previously in our group, different malonate analogues have been investigated. For example, in 1982 Wynn showed the utility of $NCCH_2COSR$ in both alkylation and Knoevenagel reactions.[13] Its greatest utility was in the selective reduction of the thiol ester to an alcohol unit which could be subsequently dehydrated to form α, β-unsaturated nitriles, as shown in Equation 20.



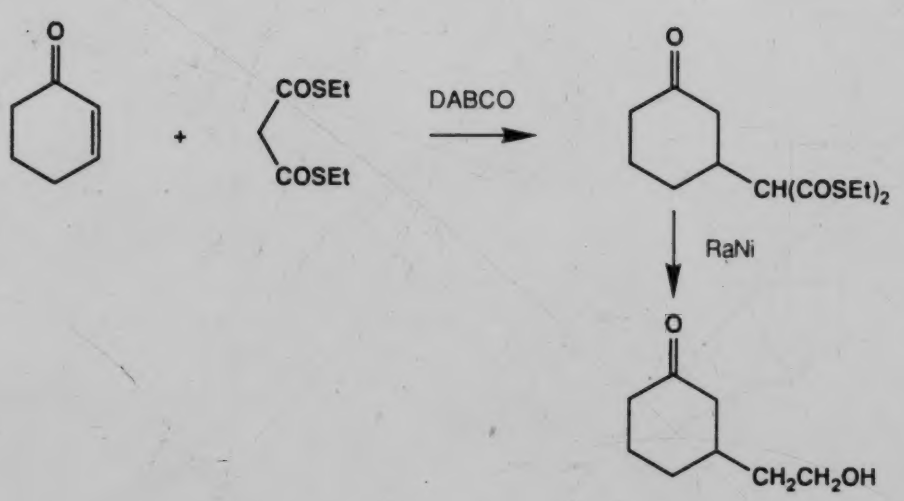
Eq. 20

The symmetrical *S,S'*-diethyl dithiolmalonate **111** was also investigated in our group and found to be a versatile reagent as it readily undergoes both alkylation and Michael addition reactions, as seen in Equations 21 and 22.[14,15] The dithiol esters produced by these reactions could be reduced with Raney-Nickel to give ethanol derivatives, thereby using *S,S'*-diethyl dithiolmalonate to overall introduce an ethanol carbanion equivalent.



111

Eq. 21



Eq. 22

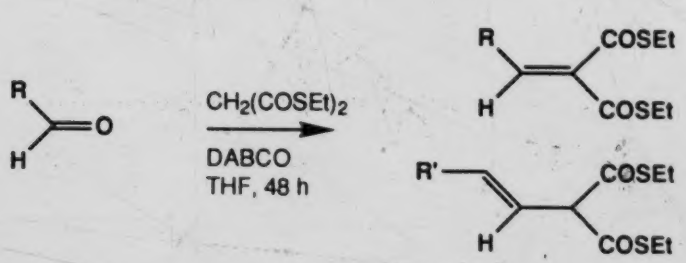
The remaining area which needed to be investigated with reagent **111** was its condensation with aldehydes and ketones and subsequent reduction of the product. The following section reports the use of *S,S'*-diethyl dithiolmalonate as a reagent for the Knoevenagel condensation, along with methods for reducing the products to the hydroxy ethyl, the 1,3-diol and the saturated dithiol ester products.

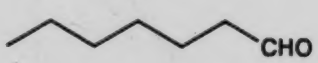
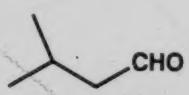
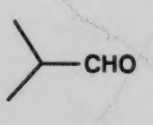
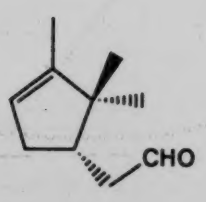
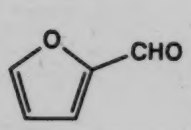
RESULTS AND DISCUSSION

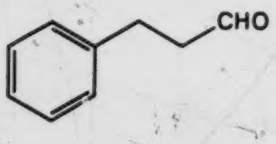
S,S'-Diethyl dithiolmalonate **111** was prepared by a method previously reported in our group.[14] Thus, malonyl dichloride and ethanethiol were mixed together in ether at room temperature and allowed to react for 16 hours. Distillation (110°C at 1.5 mm Hg) afforded the desired compound in high yields. The infrared spectrum showed a strong band at 1674 cm^{-1} for the carbonyl, typical of a thiol ester. The ^1H NMR showed three peaks, a singlet at δ 3.79 for the methylene protons adjacent to the thiol esters, as well as a quartet and a triplet for the ethyl groups at δ 2.96 (q, J = 8 Hz, 4H) and 1.14. (t, J = 8 Hz, 6H), respectivily. HRMS gave a molecular ion peak at 192.0282.

The first set of conditions which were applied to the Knoevenagel reaction were those developed by Wynn for the Knoevenagel reaction of cyanothiolacetate with carbonyl compounds.[13] In a typical experiment, 1.2 equivalents of thiol ester and 1 equivalent of DABCO were mixed together in THF for 10 minutes. Next, 1 equivalent of aldehyde was added along with a small amount of sodium sulfate to assist in the dehydration step. The mixture was stirred at room temperature under argon for 48 hours. After work-up and flash chromatography, yields ranged from 38% to 85% for a variety of different aldehydes (see Table 3).

Table 3: Knoevenagel Condensation of *S,S'*-Diethyl Dithiolmalonate with Aldehydes



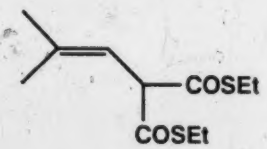
Entry	Aldehyde	Yield (%)	Ratio of α,β:β,γ isomers
1		64	2:1
2		71	4:1
3		72	1:3
4		65	10:1
5		84	-

6		63	5:3
7	$CH_3(CH_2)_{16}CHO$	38	2:1

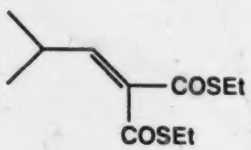
Reagent **111** reacted successfully with aliphatic aldehydes as well as with furfural. The product from the reaction of furfural and reagent **111** (Entry 5) showed the following spectral data. Infrared spectroscopy showed a strong band at 1652 cm^{-1} for the carbonyl stretches. The ^1H NMR showed the typical furan ring peaks as well as a singlet at δ 7.42 for the proton on the double bond conjugated to the thiol esters. Two sets of ethyl groups were also evident, with quartets at δ 3.04 (J = 7 Hz, 2H) and 3.14 (J = 7 Hz, 2H), and triplets at δ 1.40 (J = 7 Hz, 3H) and 1.30 (J = 7 Hz, 3H). The carbonyls on the thiol ester showed peaks in the ^{13}C NMR at δ 193 and 187 and HRMS gave the molecular ion peak at 270.0383 for the formula $C_{12}H_{14}O_3S_2$.

Furfural cleanly gave one product in the reaction mixture. However, in the remaining six examples inseparable mixtures of the α,β- and β,γ-unsaturated dithiol esters were formed. The most pronounced example of this was seen in the reaction of isobutryaldehyde and reagent **111** (Entry 3) where the major product **112** was the one involving the migration of the double bond. The migration was probably due to the steric interaction of the cisoidal functional groups across the double bond, which is highly

accentuated in the case of the product from isobutyraldehyde. The β,γ isomer **112** could be detected in the ^{1}H NMR spectrum of the mixture from the peaks at δ 4.5 (d, J = 10 Hz) for the hydrogen adjacent to the thiol esters and δ 5.5 (d, J = 10 Hz) for the hydrogen on the β,γ double bond to which the first was coupled. Also, the two methyls from the isopropyl group were shifted downfield to δ 1.7 (s, 3H) and 1.8 (s, 3H) from δ 1.06 (d, J = 7 Hz, 6H) in the α,β-unsaturated isomer **113**.



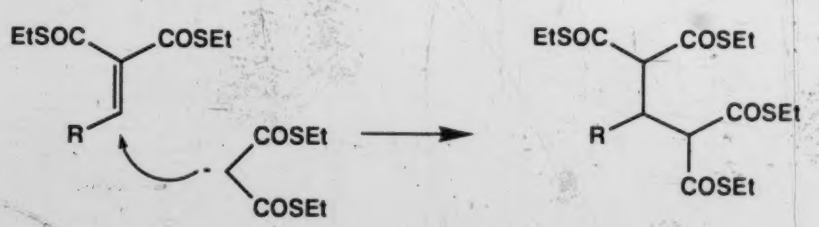
β, γ



α, β

112 **113**

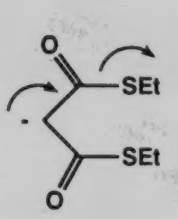
A second yet partially solvable problem of the reaction was the competing Michael addition of *S,S'*-diethyl dithiolmalonate to the newly formed product (see Equation 23). Initially, 1.5 equivalents of *S,S'*-diethyl dithiolmalonate was used in the reaction and often a large percentage of the product was that of bis-addition. Fortunately, by decreasing the amount of *S,S'*-diethyl dithiolmalonate to 1.1 or 1.2 equivalents the side product could be almost eliminated.



Eq. 23

S,S'-diethyl dithiolmalonate was found to be unreactive towards cyclohexanone at room or refluxing temperatures. This showed our reagent to be less reactive than diethyl malonate which has been shown to react with ketones, albeit in low yields.

In an attempt to improve upon the yields, several different conditions and catalysts were applied. Increasing the reaction temperature to reflux led to the partial decomposition of the *S,S'*-diethyl dithiolmalonate, along with lower yields. This decomposition probably occurred through elimination of ethanethiol from the intermediate anion, as shown below, judging from the pungent odour of the reaction mixture.



Previously in our group Han[16] used an acetone and potassium carbonate mixture to carry out a tandem alkylation and subsequent Michael addition to generate new bicyclic systems using *S,S'*-diethyl dithiolmalonate as the activating group. These conditions were applied to the reaction of reagent **111** and heptanal. Unfortunately, no product could be detected after a 20 hour reaction period.

Finally, a series of catalysts were examined. Recently in our group, enolate reactions were found to be facilitated by the addition of cerium chloride as the counter ion. Following the procedure developed by Zhu,[17]

dried cerium(III) chloride was stirred for 3 hours in THF to form a suspension of fine particles. In another dried, argon flushed flask, the enolate ion was generated by reaction of *S,S'*-diethyl dithiolmalonate and DABCO. The enolate was then transfered to the cerium chloride solution at 0°C and stirred for 1 hour further whereupon the aldehyde was added and the mixture left to react. Unfortunately, after overnight reaction only starting material was recovered, with no trace of product being detected.

The premise for using DABCO as the base in this reaction was its ability to both deprotonate the malonate derivative as well as providing a conjugate acid which could act as a protonating agent for the anion formed from the condensation. This protonation would hinder the reverse reaction from taking place. However, the possibility existed that the DABCO was interfering with the formation of the cerium complex, therefore the preceding reaction was repeated using sodium hydride as the base. Traces of the product were detected after overnight reaction, however a longer reaction time did not show any further increase in product.

Titanium tetrachloride had also been used by several groups to promote Knoevenagel condensations.[18,19] Therefore, heptanal and *S,S'*-diethyl dithiolmalonate were mixed together at 0°C in dichloromethane, followed by slow addition of titanium tetrachloride. The mixture was slowly warmed to reflux and left overnight. Unfortunately, again only a trace amount of product was formed.

Two further conditions were applied with similar resuits. Deslongchamp used cesium carbonate as a catalyst for a tandem intermolecular Michael

addition of a malonate derivative and subsequent intramolecular aldol condensation.[20] Upon mixing cesium carbonate and *S,S'*-diethyl dithiolmalonate in chloroform, a very thick suspension formed which upon subsequent addition of heptanal yielded only starting material.

Texier-Boulet and Foucaud's method of Knoevenagel condensation involved mixing the aldehyde and reagent directly to solid alumina in the absence of any solvent.[21] This method gave high yields in extremely short reaction times (3 minutes). Thus, 1 mmol each of heptanal and *S,S'*-diethyl dithiolmalonate were added to 0.3 g alumina (Merck 90 - basic), however trace product could only be detected after a twenty hour reaction period.

One final attempt at improving the reaction was tried, involving changing the ester to a bulkier, more stable group, namely a tertiary butyl group. This would hopefully permit refluxing conditions to be used to accelerate the reaction, and possibly eliminate all traces of the disubstitution product.

Therefore, *S,S'*-di-*tert*-butyl dithiolmalonate ($CH_2(COS\textit{t}\text{-}Bu)_2$ **114**) was generated in a method identical to that used for the corresponding ethyl ester, by reacting malonyl dichloride with two equivalents of *tert*-butyl mercaptan in ether. After distillation (74°C at 0.75 mm of Hg) a moderate yield of the reagent was formed. Two peaks were evident in the ^1H NMR, a large singlet at δ 1.5 for the eighteen protons on the *tert*-butyl groups, and a singlet at δ 3.6 for the two protons adjacent to the thiol esters. The ^{13}C NMR showed four signals with the carbonyls at δ 191. The HRMS gave the molecular ion peak at 248.0905.

The newly formed malonate derivative was reacted with furfural both at refluxing and room temperature utilizing conditions described previously. Unfortunately, the reagent decomposed at the higher temperature, and the bulky nature of the new reagent hindered the room temperature reaction to the extent that large amounts of starting material were still present after 3 days.

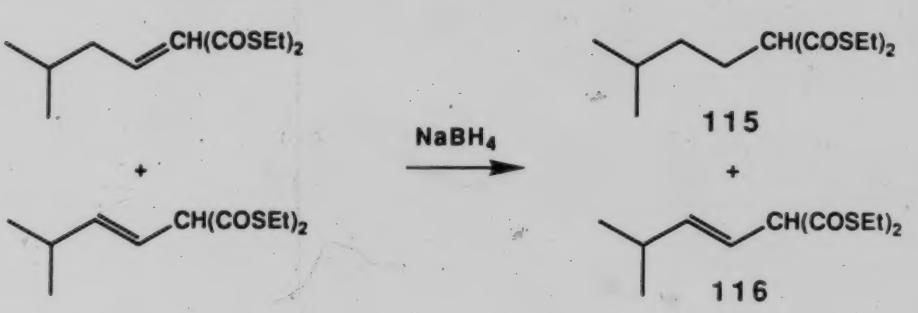
Reduction of the Unsaturated Dithiol Esters

Three different methods of utilizing the α,β-unsaturated dithiol esters were found: the selective reduction of the double bond; the complete reduction to the hydroxyethyl group; and finally reduction to the 1,3-diol. The details for these procedures are outlined below.

1. Selective Reduction

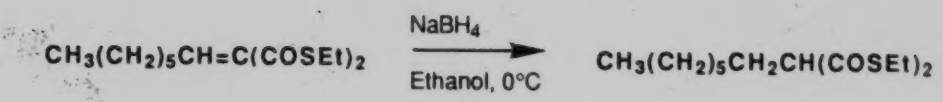
The selective reduction of the α,β–double bond was carried out on three substrates. Initially, the 4:1 isomeric mixture of the condensation products of isovaleraldehyde and *S,S'*-diethyl dithiolmalonate was reduced to an inseparable mixture of the desired saturated dithiol ester **115** and unreacted β,γ-isomer **116** (4:1 ratio), in overall 93% yield (see Equation 24). This was carried out through reaction with 1 equivalent of sodium borohydride at 0°C in ethanol for 1.5 hours. As there was no change in the amount of the minor isomer, selective 1,4-reduction of the minor isomer *via* isomerization to the α,β-isomer was not occurring under these reaction conditions. A longer reaction time could increase the chances for

isomerization, however reduction of the thiol ester groups would then become a competing reaction.



Eq.24

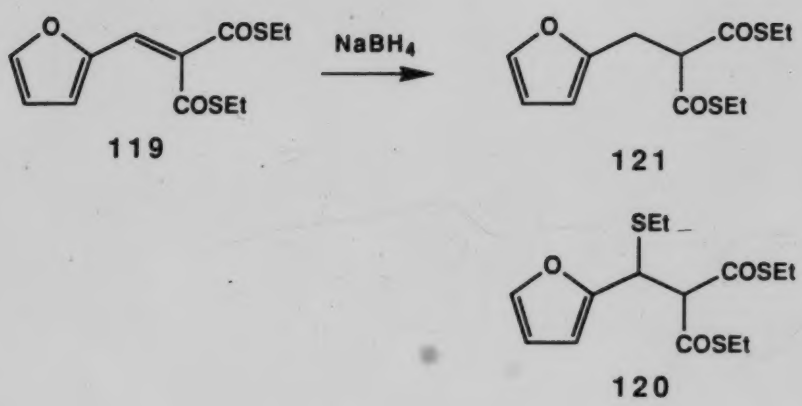
The problem of the mixture of α,β- and β,γ-isomers could be solved by passing the mixture through a short column of 10% silver nitrate adsorbed onto silica gel. The product from the condensation with heptanal was purified by this procedure, albeit in moderate yield (50%) due to partial hydrolysis of the thiol esters. The purified product was the α,β-isomer **117** with the β,γ-isomer either being selectively hydrolyzed, or isomerized to the desired compound on the column. The purified product could be selectively reduced by the above procedure in 90% yield in 20 minutes to yield compound **118** (see Equation 25). The ^{1}H NMR spectrum showed a triplet at δ 3.75 for the proton adjacent to the two thiol esters coupled to two protons showing as a quartet at δ 2.92. No olefinic protons were in evidence. Infrared spectroscopy showed a carbonyl stretch at 1699 cm^{-1}, typical of a saturated thiol ester. Mass spectroscopy gave the desired molecular ion peak at 290.1374 for the formula $C_{14}H_{26}O_2S_2$.



117 **118**

Eq. 25

The third compound utilized in this study was the furfural condensation product **119**, which did not have the added problem of being an isomeric mixture as it contains no γ proton. However, this compound, due to conjugation to the furan ring, was much slower to reduce in a 1,4 manner, allowing for the competitive reduction of the thiol ester. The ethyl mercaptan thus produced caused the formation of an unusual side product **120** generated through the 1,4-addition of the mercaptan to the starting material (see Equation 26). This could be verified by the following spectral data. The ^{1}H NMR spectrum showed three separate ethyl group peaks. Two doublets coupled to each other with a coupling constant of 11.5 Hz could be seen at δ 4.72 and 4.40, representing the protons α and β to the thiol esters. Infrared spectroscopy showed the presence of saturated thiol esters with a stretch at 1699 cm^{-1}, while mass spectroscopy confirmed the structure with a molecular ion peak at 332.0575 for the formula $C_{14}H_{20}O_3S_3$. The desired 1,4-reduction product **121** was formed in 49% yield, along with a 10% production of compound **120**. Presumably the remaining material was overreduced compound.



119 121 120

Eq. 26

In an attempt to improve upon the yield of this reduction, several different reaction conditions were examined. The solvent was changed from ethanol to methanol to try and enhance the speed of the 1,4-reduction, however the same results were obtained. Changing the temperature of the reaction from 0°C to room temperature to increase the reduction rate also did not show any improvement.

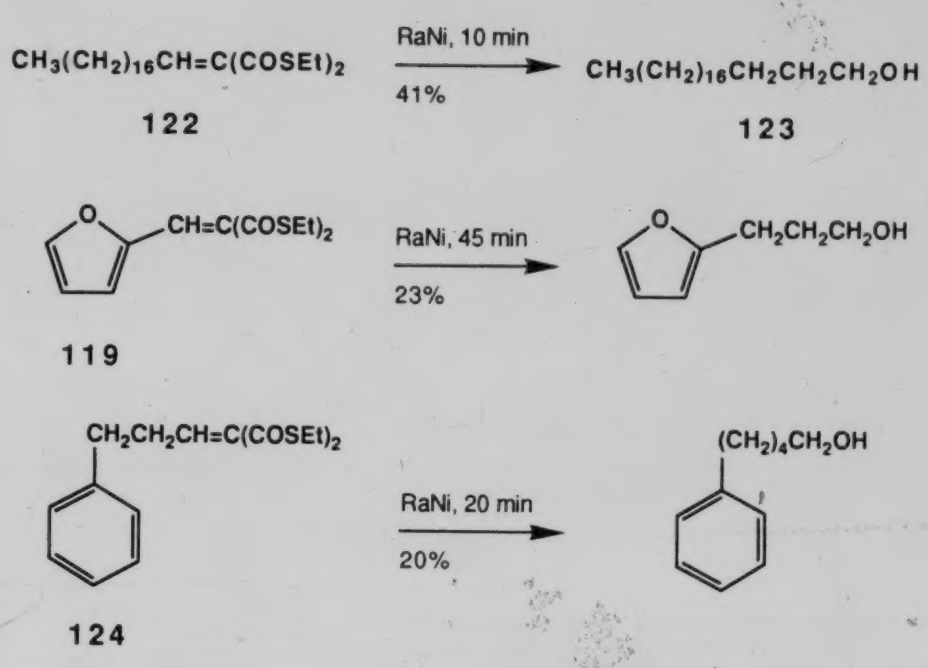
2. Raney-Nickel reduction

The saturated dithiol ester had been shown previously to be reducible to a hydroxyethyl unit using Raney-Nickel.[14] Direct Raney-Nickel reduction of the α,β-unsaturated dithiol ester was found to give the same product in low to moderate yields (see Scheme 16). For example, compound **122** was mixed with 1.3 mL of Raney-Nickel per 100 mg of substrate at room temperature in benzene for 10 minutes. After purification, spectral analysis showed that alcohol **123** had been formed in 41% yield. Infrared spectroscopy showed a broad O-H band centered at 3300 cm^{-1}, as well

the carbonyl stretch of the thiol ester was noticeably absent. The ^1H NMR spectrum showed a triplet at δ 3.65 for the 2 hydrogens adjacent to the hydroxyl group, along with a definite lack of protons from the olefin or ester. Also, there was no trace the β,γ-isomer which was present in the starting material.

Similarly, two further compounds **119** and **124** were reduced under the same reaction conditions, however in lower yields, as shown in Scheme 16. The low yields for the Raney-Nickel reductions could be attributed to many factors. First, several operations are being carried out by the Raney-Nickel: hydrogenation of the double bond, reductive cleavage of one of the thiol esters, along with complete reduction of the second thiol ester. Secondly, the aptitude of Raney-Nickel to adsorb small molecules was a problem as seen in the lower yields for the smaller molecules.

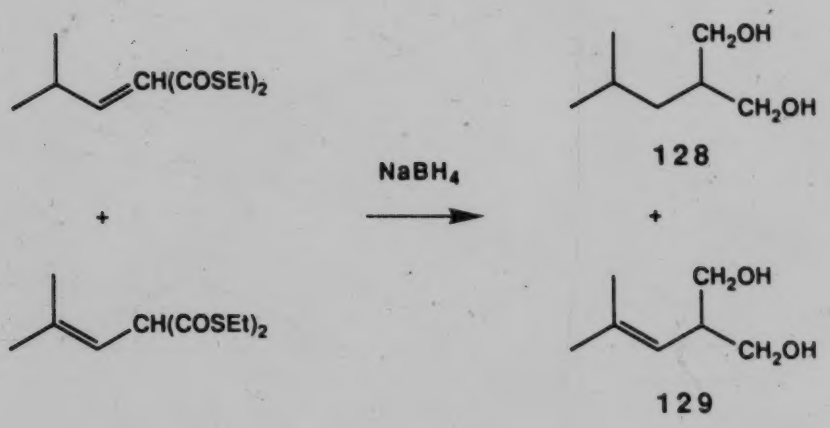
SCHEME 16



3. Complete Sodium Borohydride Reduction

The dithiol esters could be completely reduced by sodium borohydride to the 1,3-diols in reasonable yields. In a typical procedure, excess sodium borohydride is added over a period of two days to an ethanolic solution of the dithiol ester at room temperature. Yields are shown in Table 4. Compound **125**, the reduction product of the furfural condensation adduct (Entry 6) showed the following spectral data. Infrared spectroscopy showed a broad O-H band centered around 3350 cm^{-1} and the ^1H NMR spectrum showed, along with the furan ring peaks, two sets of doublets of doublets at δ 3.64 (dd, J = 7, 11 Hz, 2H) and δ 3.78 (dd, J = 4, 11 Hz, 2H) for the four protons adjacent to the hydroxyl groups. Noticeably absent were the ethyl group and olefinic protons. Mass spectroscopy showed a molecular ion peak at 156.0709 for the correct formula $C_8H_{12}O_3$.

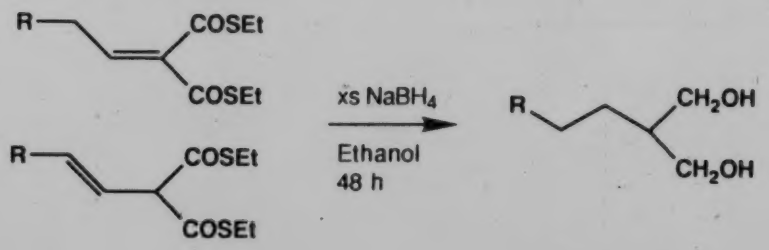
In all cases but one the β,γ-isomer was also reduced to the saturated diol, presumably *via* isomerization to the α,β-isomer. The exception was the reduction product from the isobutryaldehyde adduct (Entry 3) in which the starting material was mainly the β,γ-unsaturated isomer. Nineteen percent of the starting material (pure β,γ-isomer) was isolated from the reaction mixture. Also, the diol which was produced was a mixture (4:1) of the desired diol **128** and the diol **129** containing a double bond in the 3 position (see Equation 27).

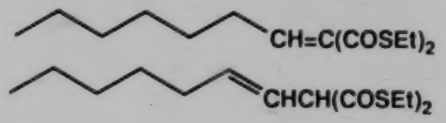
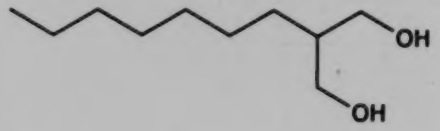


Eq. 27

In summary, *S,S'*-diethyl dithiolmalonate can be applied as a reagent for the Knoevenagel condensation reaction. The products formed, although often mixtures of two isomers, can be purified and selectively reduced to form the corresponding saturated thiol esters. Alternatively, the mixtures can be completely reduced to form the 1,3-diols using sodium borohydride or reductively cleaved to overall introduce an ethanol carbanion equivalent by the action of Raney-Nickel.

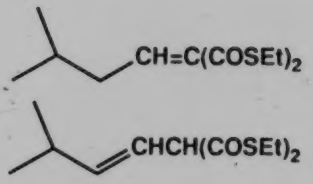
Table 4. Sodium Borohydride Reduction of the Dithiol Esters to the 1,3-Diols

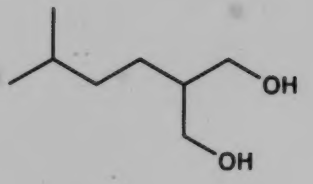


Entry	Thiol Ester	Product	Yield (%)
1			73

126

2





70

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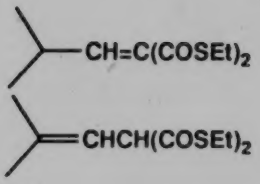
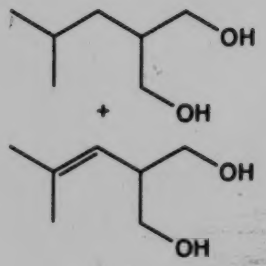
3



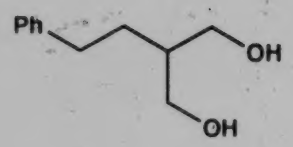


60

128 and 129

4 $PhCH_2CH_2CH=C(COSEt)_2$

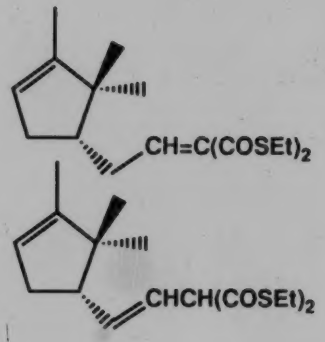
$PhCH_2CH=CHCH(COSEt)_2$

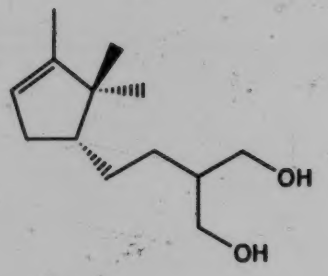


55

130

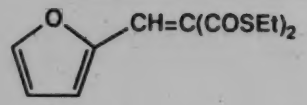
5

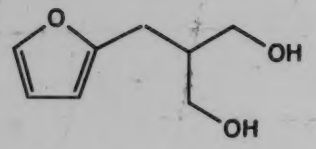




74

131

6 



84

125

EXPERIMENTAL

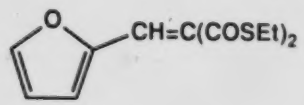
General and Materials

Refer to Chapter I, Experimental Section for a detailed description of general procedures and materials data.

General Procedure for Knoevenagel Condensation

To a dried, argon flushed flask were added THF (10 mL) and *S,S'*-diethyl dithiolmalonate (1.2 eq) and the solution cooled to 0°C. DABCO (1eq) and sodium sulfate (~0.3 g) were added and the mixture stirred for 10 minutes. Freshly distilled aldehyde (1 eq) was then added, the solution slowly warmed to room temperature and left to stir under argon for 48 hours. The reaction was then quenched with 1M HCl, extracted into dichloromethane, washed with saturated brine and dried over magnesium sulfate. The non-polar compounds could be easily purified by flash chromatography, typically using 5% ethyl acetate in petroleum ether.

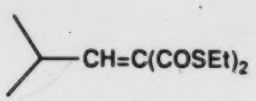
S-Ethyl 2-(ethylthio)carbonyl-3-furfuryl-2-propenethioate (119).



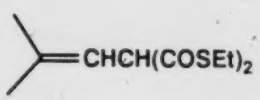
Following the general procedure, *S,S'*-diethyl dithiolmalonate (419 mg, 2.2 mmol), DABCO (0.23 g, 2.0 mmol) and furfural (0.165 mL, 2.0 mmol) were reacted together. After purification, 468 mg (87%) of the desired compound was generated, showing the following spectral data. ^{1}H NMR

(200 MHz): δ 7.60 (d, J = 1 Hz, 1H, -O-C**H**=CH), 7.42 (s, 1H, -C**H**=C(COSR)), 6.88 (d, J = 3.5 Hz, 1H, -O-CR=C**H**), 6.55 (dd, J = 1, 3.5 Hz, 1H, -O-CH=C**H**), 3.12 (q, J = 7 Hz, 2H, -SC**H**$_2$), 3.04 (q, J = 7 Hz, 2H, -SC**H**$_2$), 1.40 (t, J = 7Hz, 3H, -CH$_2$C**H**$_3$), 1.30 (t, J = 7Hz, 3H, -CH$_2$C**H**$_3$). ^{13}C NMR (100 MHz): δ 192.9 and 187.4 (C=O), 148.6 and 146.6 (-O-**C**=C), 134.4 (=**C**(COSR)$_2$), 119.0 and 112.9 (-O-C=**C**), 24.3 and 23.9 (-S**C**H$_2$), 14.4 and 14.2 (-SCH$_2$**C**H$_3$). FTIR (CCl_4 cast): 1652 (C=O), 1617 (C=C), 1597 (C=C) cm^{-1}. HRMS M$^+$: 270.0383 (calcd. for $C_{12}H_{14}O_3S_2$ 270.0384). Anal. Calcd. for $C_{12}H_{14}O_3S_2$: C, 53.31; H, 5.22; S, 23.72. Found: C, 53.43; H, 5.11; S, 23.42.

_S_-Ethyl 2-(ethylthio)carbonyl-4-methyl-2-pentenethioate (113) and _S_-Ethyl 2-(ethylthio)carbonyl-4-methyl-3-pentenethioate (114).



113

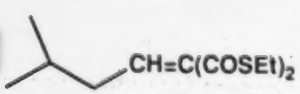


114

Following the general procedure, _S,S'_-diethyl dithiolmalonate (2.06 g, 10.7 mmol), DABCO (0.90 g, 9 mmol) and isobutryaldehyde (653 mg, 9.0 mmol) were reacted together in 60 mL THF. After purification, 1.6 g (72%) of an inseparable mixture of two isomeric compounds (ratio 2.75:1) was generated, the major (β, γ isomer) showing the following spectral data. ^{1}H NMR (200 MHz): δ 5.50 (d, J = 10 Hz, 1H, =C**H**CH(COSR)), 4.50 (d, J = 10 Hz, 1H, -CHC**H**(COSR)), 2.86 (q, J = 7 Hz, 4H, -SC**H**$_2$), 1.80 (s, 3H, =CC**H**$_3$), 1.70 (s, 3H, =CC**H**$_3$), 1.22 (t, J = 7Hz, 6H, -CH$_2$C**H**$_3$). The minor isomer showed the following NMR spectral data: δ 6.62 (d, J = 11 Hz, 1H,

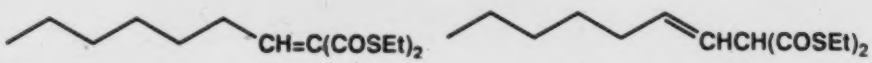
-CH=C), 3.2 (q, J = 7 Hz, 2H, -SCH$_2$), 2.94 (q, J = 7 Hz, 2H, -SCH$_2$), 1.32 (t, J = 7 Hz, 3H, -SCH$_2$CH$_3$), 1.29 (t, J = 7 Hz, 3H, -SCH$_2$CH$_3$), 1.06 (d, J = 7 Hz, 6H, -CH(CH$_3$)$_2$). The mixture showed the following spectral data. FTIR: 1697 (C=O), 1668 (C=C-C=O) cm^{-1}. HRMS M$^+$: 246.0740 (calcd. for $C_{11}H_{18}O_2S_2$ 246.0748). Anal. Calcd. for $C_{11}H_{18}O_2S_2$: C, 53.63; H, 7.36; S, 26.03. Found: C, 53.38; H, 7.06; S, 26.22.

_S_-Ethyl 2-(ethylthio)carbonyl-5-methyl-2-hexenethioate and _S_-Ethyl 2-(ethylthio)carbonyl-5-methyl-3-hexenethioate.



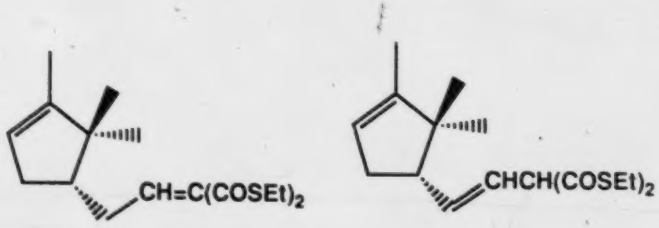
Following the general procedure, _S,S'_-diethyl dithiolmalonate (231 mg, 1.2 mmol), DABCO (0.11 g, 0.1 mmol) and isovaleraldehyde (0.11 mL, 1 mmol) were reacted together in 10 mL THF. After purification, (flash chromatography, 3% ether / petroleum ether) 190 mg (71%) of an inseparable mixture of two isomeric compounds (ratio 4:1) was generated, the major (α, β isomer) showing the following spectral data. FTIR (CH_2Cl_2 cast): 1667 (C=C-C=O) with a shoulder at ~1690 (C=O) cm^{-1}. HRMS M$^+$: 260.0903 (calcd. for $C_{12}H_{20}O_2S_2$ 260.0905). The major isomer showed the following ^{1}H NMR (200 MHz) data: δ 6.80 (t, J = 6.5 Hz, 1H, -CH=C), 3.0 (m, 4H, -SCH$_2$), 2.14 (dd, J = 6.5, 7.5 Hz, 2H, -CH$_2$C=C), 1.8 (m, 1H, -CH(CH$_3$)$_2$), 1.30 (m, 6H, -SCH$_2$CH$_3$), 0.98 (d, J = 7 Hz, 6H, -CH(CH$_3$)$_2$). The minor isomer displayed the following set of peaks in the ^{1}H NMR (200 MHz) spectrum: δ 5.72 (m, 1H, =CH), 4.28 (m, 1H, =CH), 1.02 (d, J = 7 Hz, -CH(CH$_3$)$_2$).

S-Ethyl 2-(ethylthio)carbonyl-2-nonenethioate and S-Ethyl 2-(ethylthio)carbonyl-3-nonenethioate.



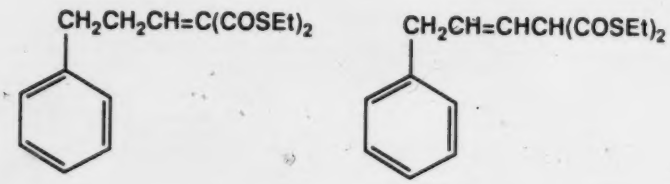
Following the general procedure, *S,S'*-diethyl dithiolmalonate (216 mg, 1.2 eq), DABCO (0.11 g, 1.0 eq) and heptanal (0.13 mL, 0.94 mmol) were reacted together in 10 mL THF. After purification, 179 mg (64%) of a mixture of two isomeric compounds (ratio 2:1) was generated. The mixture showed the following spectral data. FTIR (CCl_4 cast): 1666 (C=C-C=O) with a shoulder at ~1690 (C=O) cm^{-1}. HRMS M^+: 288.1222 (calcd. for $C_{14}H_{24}O_2S_2$ 288.1218). The minor isomer (β, γ isomer) showed the following ^1H NMR (200 MHz) spectral data: δ 5.78 (m, 1H, =C**H**), 4.3 (m, 1H, =C**H**). The major isomer could be isolated from the minor isomer by passing the mixture through a short 10% silver nitrate/silica gel gravity column. The pure α, β isomer displayed the following ^1H NMR (200 MHz) spectral data: δ 6.94 (t, *J* = 8 Hz, 1H, -C**H**=C), 2.98 (two overlapping q, *J* = 7 Hz, 4H, -SC**H**$_2$), 2.35 (q, *J* = 7 Hz, 2H, -C**H**$_2$C=C), 1.35 (two overlapping t, *J* = 7 Hz, 6H, -SCH$_2$C**H**$_3$, overlapping m, 8H), 0.92 (m, 3H, -(CH$_2$)$_5$C**H**$_3$).

S-Ethyl 2-(ethylthio)carbonyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)-2-butenethioate and S-Ethyl 2-(ethylthio)carbonyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)-3-butenethioate.



Following the general procedure, *S,S'*-diethyl dithiolmalonate (189 mg, 1.0 mmol), DABCO (0.11 g, 1.0 mmol) and campholenic aldehyde (155.8 mg, 1 mmol) were reacted together in 10 mL THF. After purification, 217 mg (65%) of an inseparable mixture of two isomeric compounds (ratio 10:1) was generated and showed the following spectral data. FTIR: 1697 (C=O), 1669 (C=C-C=O) cm^{-1}. HRMS $(M\text{-}SCH_2CH_3)^+$: 265.1258 (calcd. for $C_{15}H_{21}O_2S$ 265.1262). The major (α, β isomer) showed the following ^1H NMR (200 MHz) spectral data: δ 6.88 (t, *J* = 8 Hz, 1H, -C**H**=C$(COSR)_2$), 5.75 (m, 1H, -C**H**=C), 2.95 (m, 4H, -SC**H**$_2$), 2.45 (m, 2H, =C-C**H**$_2$), 2.30 (m, 2H, -C**H**$_2$C=C), 1.95 (m, 1H), 1.60 (s, 3H, -C**H**$_3$), 1.25 (m, 6H, -SCH$_2$C**H**$_3$), 0.86 (s, 3H, -C(C**H**$_3)_2$)), 0.78 (s, 3H, -C(C**H**$_3)_2$)). The minor isomer showed the following ^1H NMR (200 MHz) spectral data: δ 5.8 (m, 1H, =C**H**), 4.33 (m, 1H, =C**H**), 4.0 (m, 1H, -C**H**$(COSEt)_2$), 0.98 (s, 3H, -C**H**$_3$), 0.75 (s, 3H, -C**H**$_3$).

S-Ethyl 2-(ethylthio)carbonyl-5-phenyl-2-pentenethioate (124) and S-Ethyl 2-(ethylthio)carbonyl-5-phenyl-3-pentenethioate.



Following the general procedure, *S,S'*-diethyl dithiolmalonate (206 mg, 1.1 mmol), DABCO (0.10 g, 1.0 mmol) and dihydrocinnamaldehyde (0.12 mL, 0.9 mmol) were reacted together. After purification, 173 mg (63%) of the desired compound was generated as a mixture of two isomers (ratio 5:3) showing the following spectral data. FTIR (CH_2Cl_2 cast): 1697 (C=C-

C=O), 1665 (C=O) cm^{-1}. HRMS M^+: 308.0904 (calcd. for $C_{16}H_{20}O_2S_2$ 308.0905). Anal. Calcd. for $C_{16}H_{20}O_2S_2$: C, 62.31; H, 6.53; S, 20.79. Found: C, 62.16; H, 6.77; S, 20.90. The major (α, β isomer) showed the following ^{1}H NMR (200 MHz) spectral data: δ 7.25 (m, 5H, Ar), 6.88 (t, J = 7 Hz, 1H, -C=C**H**), 3.0 (m, 4H, -SC**H**$_2$), 2.68 (m, 2H, ArC**H**$_2$-), 1.8 (m, 2H, ArCH$_2$C**H**$_2$-), 1.3 (m, 6H, -SCH$_2$C**H**$_3$). The minor isomer displayed the following peaks in the ^{1}H NMR (200 MHz): δ 5.88 (m, 1H, =C**H**), 4.34 (m, 1H, =C**H**), 4.0 (d, J = 10 Hz, -C**H**(COSEt)$_2$).

_S_-Ethyl 2-(ethylthio)carbonyl-2-icosenethioate (122) and _S_-Ethyl 2-(ethylthio)carbonyl-3-icosenethioate.

$CH_3(CH_2)_{16}CH=C(COSEt)_2$ $CH_3(CH_2)_{15}CH=CHCH(COSEt)_2$

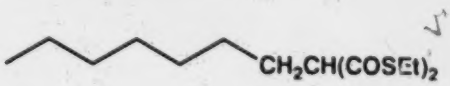
Following the general procedure, *S,S'*-diethyl dithiolmalonate (288 mg, 1.5 mmol), DABCO (0.14 g, 1.2 mmol) and octadecanal (333 mg, 1.25 mmol) were reacted together. After purification, 221 mg (38%) of the desired compound was generated as a 2:1 mixture of inseparable isomers showing the following spectral data. FTIR: 1690 (C=O), 1662 (C=C-C=O) cm^{-1}. HRMS M^+: 442.2958 (calcd. for $C_{25}H_{46}O_2S_2$ 442.2949). The major isomer (α, β) showed the following ^{1}H NMR (200 MHz) spectral data: δ 6.88 (t, J = 7 Hz, 1H, -C=C**H**), 2.9 (m, 4H, -SC**H**$_2$), 2.32 (m, 2H), 1.25 (bs, 36H, -(C**H**$_2$)$_{16}$CH$_3$, -SCH$_2$C**H**$_3$), 0.88 (vt, J = 6 Hz, 3H, -(CH$_2$)$_{16}$C**H**$_3$). The minor isomer displayed the following peaks in the ^{1}H NMR (200 MHz) spectrum: δ 5.75 (m, 1H, =C**H**), 4.29 (m, 1H, =C**H**), 3.95 (m, 1H, -C**H**(COSEt)$_2$).

Selective Reduction using Sodium Borohydride

General procedure

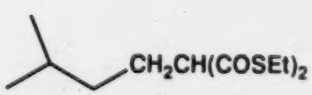
To a cooled (0°C) stirring solution of the dithiol ester in 95% ethanol was added 1 molar equivalent of sodium borohydride. After stirring at 0°C for one hour, the reaction was quenched with saturated ammonium chloride solution and extracted into dichloromethane. The organic extracts were washed with water and brine and then dried over magnesium sulfate.

***S*-Ethyl 2-(ethylthio)carbonylnonanethioate (118).**



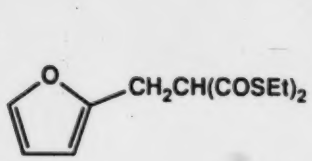
Following the general procedure, 139.8 mg (0.48 mmol) of the condensation product between reagent **111** and heptaldehyde was reacted with sodium borohydride (18 mg, 1 mol eq) in 4 mL ethanol. Flash chromatography (10% ether / petroleum ether) produced 132 mg (94%) of the following compound. ^{1}H NMR (200 MHz): δ 3.75 (t, *J* = 7 Hz, 1H, -C**H**(COSR)$_2$), 2.92 (q, *J* = 7 Hz, 4H, -SC**H**$_2$), 1.95 (bq, *J* = 7 Hz, 2H, -C**H**$_2$C-CH(COSR)$_2$), 1.28 (t, *J* = 7 Hz, 6H, -SCH$_2$C**H**$_3$, overlapping m, 10 H), 0.87 (vt, *J* = 7 Hz, 3H, -(CH$_2$)$_5$C**H**$_3$). FTIR: 1699 (C=O) cm^{-1}. HRMS M$^+$: 290.1374 (calcd. for $C_{14}H_{26}O_2S_2$ 290.1374).

***S*-Ethyl 2-(ethylthio)carbonyl-5-methylhexanethioate (115).**

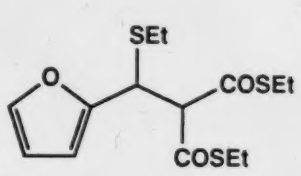


Following the general procedure, 116 mg (0.45 mmol) of the isomeric mixture of compounds generated from the reaction of reagent **111** with isovaleraldehyde was reacted with sodium borohydride (4 mg, 1 mol eq) in 5 mL ethanol. Flash chromatography (5% ethyl acetate / petroleum ether) produced 109 mg (94%) of a mixture of two inseparable compounds (4:1 ratio), one being the desired compound and the other being the β, γ-unsaturated starting material. The desired product showed the following peaks in the ^{1}H NMR (200 MHz) spectrum: δ 3.72 (t, *J* = 7 Hz, 1H, -C**H**(COSR)$_2$), 2.92 (q, *J* = 7 Hz, 4H, -SC**H**$_2$), 1.96 (m, 2H, -C**H**$_2$CCH(COSR)$_2$), 1.55 (m, 1H, -C**H**(CH$_3$)$_2$), 1.25 (q, *J* = 7 Hz, 6H, -SCH$_2$C**H**$_3$, overlapping m, 2H), 0.88 (d, *J* = 7 Hz, 6H, -CH(C**H**$_3$)$_2$). The inseparable mixture showed the following spectral data. FTIR: 1699 (C=O) cm^{-1}. HRMS M$^+$: 262.1052 (calcd. for $C_{12}H_{22}O_2S_2$ 262.1061), for the desired compound.

S-Ethyl 2-(ethylthio)carbonyl-3-furfurylpropanethioate (121) and S-Ethyl 2-(ethylthio)carbonyl-3-furfuryl-3-(ethylthio)propane-thioate (120).



121



120

Following the general procedure, 213 mg (0.92 mmol) of the adduct formed from the reaction of reagent **111** with furfuraldehyde was reacted with sodium borohydride (30 mg, 1 mol eq) in 5 mL of ethanol. Flash chromatography (5% ether / petroleum ether) produced 104 mg (49%) of

the desired compound. Also isolated (24 mg, 9%) was compound **120**. The major compound showed the following spectral data. ^{1}H NMR (400 MHz): δ 7.30 (dd, *J* = 3, 0.5 Hz, 1H, -O-C**H**=CH), 6.25 (dd, *J* = 3, 2 Hz, 1H, -O-CH=C**H**), 6.05 (dd, *J* = 2, 0.5 Hz, 1H, -O-CH=CHC**H**), 4.18 (t, *J* = 7.5 Hz, 1H, -C**H**(COSR)$_2$), 3.28 (d, *J* = 8 Hz, 2H, -C**H**$_2$CH), 2.92 (dq, *J* = 3, 7 Hz, 4H, -SC**H**$_2$), 1.25 (t, *J* = 7.5 Hz, 6H, -SCH$_2$C**H**$_3$). FTIR: 1697 (C=O) cm^{-1}. HRMS M$^+$: 272.0541 (calcd. for $C_{12}H_{16}O_3S_2$ 272.0541).

The by-product **120** showed the following spectral properties. ^{1}H NMR (400 MHz): δ 7.38 (dd, *J* = 1, 2 Hz, 1H, -O-C**H**=CH), 6.26 (dd, *J* = 2, 3 Hz, 1H, -O-CH=C**H**), 6.18 (dd, *J* = 1, 3 Hz, 1H, -O-CH=CHC**H**), 4.72 (d, *J* = 11.5 Hz, 1H, -C**H**CH), 4.40 (d, *J* = 11.5 Hz, 1H, -C**H**(COSR)$_2$), 3.0 (dq, *J* = 2, 7.5 Hz, 2H, -SC**H**$_2$CH$_3$), 2.78 (m, 2H, -SC**H**$_2$), 2.46 (m, 2H, -SC**H**$_2$), 1.30 (t, *J* = 7.5 Hz, 3H, -SCH$_2$C**H**$_3$), 1.18 (t, *J* = 7.5 Hz, 3H, -SCH$_2$C**H**$_3$), 1.10 (t, *J* = 7.5 Hz, 3H, -SCH$_2$C**H**$_3$). FTIR: 1699 (C=O) cm^{-1}. HRMS M$^+$: 332.0575 (calcd. for $C_{14}H_{20}O_3S_3$ 332.0575).

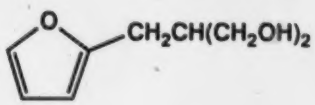
Complete Sodium Borohydride Reduction

General Procedure

The dithiol ester was dissolved in 98% ethanol (5 mL / 100 mg) and 2 molar equivalents of sodium borohydride were added. The mixture was stirred at room temperature for 48 hours, with periodical addition of small amounts of sodium borohydride (~2 molar equivalents every 12 hours). The reaction was worked up avoiding contact with water as the products were often water soluble. Therefore, the crude reaction mixture was

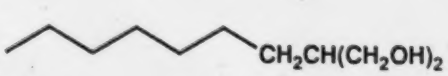
concentrated, dissolved in ether and the borate salts filtered off. After reconcentrating, the oils were subjected to flash chromatography using a very short column and unreacted starting material removed using 10% ether / petroleum ether. The product was then washed off the column with pure ether.

3-Furfuryl-2-hydroxymethyl-1-propanol (125).



Following the general procedure, 104 mg (0.39 mmol) of the dithiol ester were dissolved in 5 mL of ethanol with excess sodium borohydride and stirred for 48 hours. After workup, 51 mg (84%) of the diol was produced and showed the following spectral properties. ^{1}H NMR (200 MHz): δ 7.30 (dd, *J* = 2, 0.5 Hz, 1H, -O-C**H**=CH), 6.28 (dd, *J* = 3, 0.5 Hz, 1H, -O-CH=CHC**H**), 6.02 (dd, *J* = 2, 3 Hz, 1H, -O-CH=C**H**), 3.78 (dd, *J* = 4, 11 Hz, 2H, -C**H**$_2$OH), 3.64 (dd, *J* = 7, 11 Hz, 2H, -C**H**$_2$OH), 3.08 (bs, 2H, -O**H**), 2.68 (d, *J* = 7 Hz, 2H, -C**H**$_2$CH), 2.1 (m, 1H, -CH$_2$C**H**). FTIR: 3330 (O-H), 1030 (C-O) cm^{-1}. HRMS M$^+$: 156.0790 (calcd. for $C_8H_{12}O_3$ 156.0786).

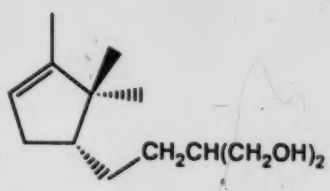
2-Hydroxymethyl-1-nonanol (126).



Following the general procedure, 89.6 mg (0.31 mmol) of the isomeric mixture of dithiol esters were dissolved in 5 mL of ethanol with excess sodium borohydride and stirred for 48 hours. After workup, 39 mg (73%)

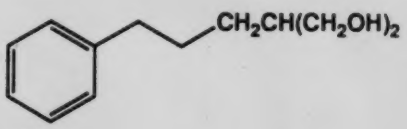
of the diol was produced and showed the following spectral properties. ^{1}H NMR (200 MHz): δ 3.85 (dd, *J* = 4, 10 Hz, 2H, -C**H**$_2$OH), 3.68 (dd, *J* = 7, 10 Hz, 2H, -C**H**$_2$OH), 2.52 (bs, 2H, -O**H**), 1.78 (m, 1H, -CH$_2$C**H**), 1.20 (m, 12H, -(C**H**$_2$)$_6$CH$_3$), 0.90 (m, 3H, -(CH$_2$)$_6$C**H**$_3$). FTIR (CCl_4 cast): 3330 (O-H), 1035 (C-O) cm^{-1}. HRMS (M - H_2O)$^+$: 156.1509 (calcd. for $C_{10}H_{20}O$ 156.1514); CIMS (M + NH_4)$^+$: 192.

2-Hydroxymethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-1-butanol (131).



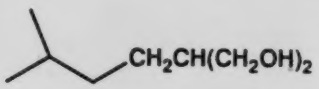
Following the general procedure, 73 mg (0.21 mmol) of the mixture of isomeric dithiol esters were dissolved in 5 mL of ethanol with excess sodium borohydride and stirred for 48 hours. After workup *via* bulb to bulb distillation (70°C, 3 mm Hg) of the crude product gave 33 mg (74%) of the diol which showed the following spectral properties. ^{1}H NMR (400 MHz): δ 5.4 (s, 1H, -C**H**=C), 3.86 (m, 2H, -C**H**$_2$OH), 3.70 (m, 2H, -C**H**$_2$OH), 2.15 and 2.30 (bs, 2H, -OH), 1.78 (m, 2H, -C**H**C=CH), 1.70 (m, 1H, -C**H**(CH$_2$OH)$_2$), 1.62 (s, 3H, -CH=CC**H**$_3$), 1.48 (m, 1H, -CH$_2$C**H**), 1.25 (m, 4H, -C**H**$_2$C**H**$_2$), 0.98 (s, 3H, -C(C**H**$_3$)$_2$), 0.78 (s, 3H, -C(C**H**$_3$)$_2$). FTIR: 3350 (O-H), 1035 (C-O) cm^{-1}. HRMS M$^+$: 212.1774 (calcd. for $C_{13}H_{24}O_2$ 212.1776).

2-Hydroxymethyl-5-phenyl-1-pentanol (130).



Following the general procedure, 65 mg (0.21 mmol) of the isomeric mixture of dithiol esters were dissolved in 5 mL of ethanol with excess sodium borohydride and stirred for 48 hours. After workup, 23 mg (55%) of the diol was produced along with 15 mg (23%) of an unreacted mixture of starting material. The diol showed the following spectral properties. ^{1}H NMR (200 MHz): δ 7.24 (m, 5H, Ar), 3.80 (dd, J = 3.5, 10 Hz, 2H, -C**H**$_2$OH), 3.64 (dd, J = 7, 10 Hz, 2H, -C**H**$_2$OH), 2.80 (bs, 2H, -O**H**), 2.64 (t, J = 8 Hz, 2H, -C**H**$_2$Ar), 2.0 (m, 1H), 1.70 (m, 2H), 1.28 (m, 2H). FTIR (CCl_4 cast): 3360 (O-H), 1030 (C-O) cm^{-1}. HRMS M$^+$: 194.1304 (calcd. for $C_{12}H_{18}O_2$ 194.1307).

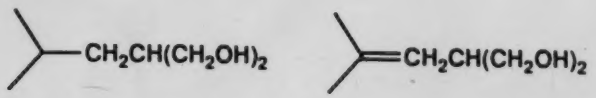
2-Hydroxymethyl-5-methyl-1-hexanol (127).



Following the general procedure, 95 mg (0.33 mmol) of the isomeric mixture of dithiol esters were dissolved in 5 mL of ethanol with excess sodium borohydride and stirred for 48 hours. After workup, 37 mg (70%) of the diol was produced, and showed the following spectral properties. ^{1}H NMR (200 MHz): δ 3.78 (dd, J = 4, 10 Hz, 2H, -C**H**$_2$OH), 3.62 (dd, J = 7, 10 Hz, 2H, -C**H**$_2$OH), 2.40 (bs, 2H, -O**H**), 1.84 (m, 1H, -C**H**(CH$_2$OH)$_2$),

1.55 (m, 1H, -C**H**$(CH_3)_2$), 1.24 (m, 4H, -CH_2CH_2), 0.90 (d, J = 8 Hz, 6H, -$CH(CH_3)_2$). FTIR: 3260 (O-H), 1099 (C-O) cm^{-1}. CIMS $(M + NH_4)^+$: 164.

2-Hydroxymethyl-4-methyl-1-pentanol (128) and 2-Hydroxymethyl-4-methyl-3-penten-1-ol (129).



128 **129**

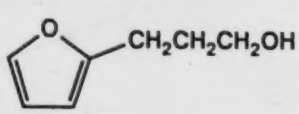
Following the general procedure, 87 mg (0.35 mmol) of the isomeric mixture of dithiol esters were dissolved in 5 mL of ethanol with excess sodium borohydride and stirred for 48 hours. After workup, 28 mg (60%) of an inseparable mixture of two diols (2:1) was produced. The major product was the desired diol and the minor was the diol containing a double bond in the 3 position. Also isolated was 17 mg (19%) of the unreduced β,γ-unsaturated starting material. The minor diol showed the following spectral properties. ^{1}H NMR (200 MHz): δ 3.7 (m, -CH_2OH), 0.90 (d, J = 7 Hz, 2H, -$CH(CH_3)$). The major diol showed the following peaks in the ^{1}H NMR spectrum: δ 4.80 (dm, J = 9 Hz, 1H, -C**H**=$C(CH_3)$), 3.7 (m, -CH_2OH), 1.74 (d, J = 1 Hz, 6H, -CH=$C(CH_3)$), 1.72 (d, J = 1 Hz, 6H, -CH=$C(CH_3)$). The mixture showed the following spectral data. FTIR (CCl_4 cast): 3280 (O-H), 1029 (C-O) cm^{-1}. CIMS $(M + NH_4)^+$: 148. The recovered β,γ-unsaturated starting material showed the following peaks in the ^{1}H NMR (200 MHz) spectrum: δ 5.52 (dm, J = 10 Hz, 1H, =C**H**), 4.54 (d, J = 10 Hz, 1H, -C**H**$(COSEt)_2$), 2.90 (q, J = 7 Hz, 4H, -SCH_2), 1.82 (d, J = 2 Hz, 3H, =CCH_3), 1.70 (d, J = 2 Hz, 3H, =CCH_3), 1.25 (t, J = 7 Hz, 6H, -SCH_2CH_3).

Raney-Nickel Reduction

General Procedure

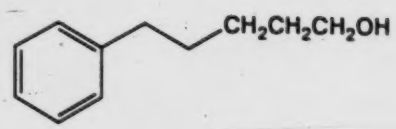
The dithiol ester was dissolved in a small amount of benzene (~1mL/100mg substrate) and stirred under argon. Acid washed W-2 Raney-Nickel (1.3 mL / 100 mg compound) was added and the mixture stirred for 30-45 minutes, after which time it was carefully filtered and washed with ethanol and then ether. Concentration and flash chromatography (50% ether / petroleum ether) produced the alcohol.

3-Furfuryl-1-propanol.



Following the general procedure, 302 mg (1.11 mmol) of the diester was dissolved in 5 mL of ethanol, followed by the addition of 5 mL of Raney-Nickel in benzene (5mL). The mixture was stirred for 45 minutes and then worked up to produce 33 mg (23%) of the alcohol. ^{1}H NMR (200 MHz): δ 7.28 (m, 1H, -O-C**H**=CH), 6.26 (m, 1H, -O-CH=CHC**H**), 6.0 (m, 1H, -O-CH=C**H**), 3.66 (t, J = 7 Hz, 2H, -C**H**$_2$OH), 2.74 (t, J = 7 Hz, 2H, fur-C**H**$_2$), 1.96 (q, J = 7 Hz, 2H, -C**H**$_2$CH$_2$OH), 1.52 (bs, 1H, -O**H**). FTIR: 3350 (O-H), 1060 (C-O) cm^{-1}. HRMS M$^+$: 126.0678 (calcd. for $C_7H_{10}O_2$ 126.0684).

5-Phenyl-1-pentanol.



Following the general procedure, 140 mg (0.45 mmol) of the diester was dissolved in 2 mL of ethanol and 1.9 mL of Raney-Nickel in 5 mL of benzene was added. The mixture was stirred for 20 minutes and then worked up, to produce 20 mg (20%) of the alcohol. ^{1}H NMR (200 MHz): δ 7.20 (m, 5H, Ar), 3.62 (t, J = 7 Hz, 2H, -C**H**$_2$OH), 2.64 (t, J = 7 Hz, 2H, Ar-C**H**$_2$), 1.50 (m, 7H). FTIR: 3330 (O-H) cm^{-1}. HRMS M$^+$: 164.1201 (calcd. for $C_{11}H_{16}O$ 164.1201). The ^{1}H NMR was identical to that reported previously for this compound.[23]

1-Icosanol (123).

$$CH_3(CH_2)_{16}CH_2CH_2CH_2OH$$

Following the general procedure, 87 mg (0.19 mmol) of the diester was dissolved in 2 mL of benzene. Raney-Nickel (1.1 mL) in 5 mL of benzene was then added and the mixture was stirred for 10 minutes, and then worked up, to produce 21 mg (41%) of the alcohol as a pure white solid (m.p. = 58-61°C). ^{1}H NMR (200 MHz): δ 3.65 (t, 2H, -C**H**$_2$OH), 1.56 (m, 2H, -C**H**$_2$CH$_2$OH), 1.26 (m, 35H), 0.88 (m, 3H, -CH$_2$C**H**$_3$). FTIR: 3300 (O-H) cm^{-1}. HRMS (M - H_2O)$^+$: 280.3138 (calcd. for $C_{20}H_{40}$ 280.3130). The ^{1}H NMR was identical to that reported previously for this compound.[23]

REFERENCES

1. Trost, B.; Latimer, L. H., *J. Org. Chem.*, **43**, 1031 (1978).
2. Baxter, J. G.; Davis, P.; Ponsford, R. J.; Southgate, R., *Tetrahedron Lett.*, **21**, 5071 (1980).
3. Dale, A. J.; Froyen, P., *Acta. Chem. Scand.*, **24**, 3772 (1970).
4. Bestmann, H. J. ; Saalbaum, H., *Bull. Soc. Chim. Belg.*, **88**, 951 (1979).
5. Bestmann, H. J.; Schmid, G.; Sandmeier, D., *Chem. Ber.*, **113**, 912 (1980).
6. Schaumann, E.; Fittkau, S., *Bull. Soc. Chim. Belg.*, **94**, 463 (1985).
7. Keck, G. E.; Boden, E. P.; Mabury, S. A., *J. Org. Chem.*, **50**, 709 (1985).
8. Keck, G. E.; Boden, E. P.; Wiley, M. R., *J. Org. Chem.*, **54**, 896 (1989).
9. Wadsworth Jr., W. S.; Emmons, W. D., *J. Am. Chem. Soc.*, **83**, 1733 (1961).
10. Arbuzov, A. E.; Razumov, A. F., *J. Russ. Phys. Chem. Soc.*, **61**, 623 (1929).
11. Liu, H.J.; Bukownik, R. R. ; Pednekar, P. R., *Synth. Commun.*, **11**, 599 (1981).
12. House, H. O. in *Knoevenagel reference*; W. A. Benjamin, Inc., Menlo Park, California, 1972, p. 646.
13. Liu, H. J.; Wynn, H., *Tetrahedron Lett.*, **23**, 3151 (1982).
14. Liu, H. J.; Lai, H. K., *Can. J. Chem.*, **57**, 2522 (1979).
15. Liu, H. J.; Oppong, I. V., *Can. J. Chem.*, **60**, 94 (1982).
16. Han, Y., Personal communication.

17. Zhu, B.Y., Personal communication.

18. Lehnert, W., *Tetrahedron*, **30**, 301 (1974).

19. Lange, J.; Kanabus-Kaminska, J. M. ; Kral, A., *Synth. Commun.*, **10**, 473 (1980).

20. Lavallee, J. F.; Deslongchamps, P., *Tetrahedron Lett.*, **29**, 6033 (1988).

21. Texier-Boullet, F.; Foucaud, A., *Tetrahedron Lett.*, **23**, 4927 (1982).

22. Weast, R.C., Editor, *Handbook of Chemistry and Physics, 59th Edition,*; CRC Press Inc., Boca Raton, Florida, 1978, p. C-532.

23. Pouchert, C. J., *The Aldrich Library of NMR Spectra*; Aldrich Chemical Co., Inc., Milwaukee, WI, 1983.